STR SEARCH for claim 3 & chemical names in claim 2

HUI 09/628,803

=> d his

(FILE 'HOME' ENTERED AT 13:45:52 ON 06 DEC 2000)

FILE 'REGISTRY' ENTERED AT 13:46:02 ON 06 DEC 2000

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L1         55091 S NC5-NC5/ES
L2        445364 S NC4-C6/ES
L3          1573 S L1 AND L2
L4           548 S L3 AND CL/ELS
L5           272 S L4 AND NRS=2
L6           272 S L5 AND NR=4
L7            99 S L6 AND 7-CHLORO-1,8-NAPHTHYRIDIN-2-YL
L8            94 S L7 NOT (F OR BR OR S)/ELS
L9            77 S L7 NOT CARBAMIC
L10           10 S L9 AND HEXYL
L11            3 S L10 AND HYDROXY
L12           67 S L9 NOT L10
L13            0 S BUTYRATE AND L12
L14            0 S L12 AND ACETAMIDOBUTYRATE
L15            0 S L12 AND ACETAM
L16            1 S L12 AND ACETAM?
L17            0 S L12 AND ?BUTYRAT?
L18            0 S L12 AND BUTYRAT?
L19            3 S L12 AND    C22 H19 CL N4 O4/MF
L20       302585 S NC4/ESS AND NC5/ESS
L21       260788 S L20 AND O/ELS
L22              STR
L23           25 S L22 SSS SAM SUB=L21
L24           477 S L22 SSS FUL SUB=L21
                SAVE L24 HUI803R/A
```

2-(7-chloro-1,8-naphthyridin-2yl)-3-(5-methyl-5-hydroxy-2-oxohexyl)-1-isoindolinone

← answer set w/ the other 2 cpds

477 cpds for STR of L22

FILE 'HCAPLUS' ENTERED AT 14:16:49 ON 06 DEC 2000

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L25          476 S L24
L26            2 S L11
L27            3 S L19
L28         9676 S STAMMER? OR SPEECH? OR STUTTER? OR TALK? OR ?SPEAK?
L29            0 S L28 AND L25-27
L30        13877 S (.GAMMA.AMINOBUTYRIC ACID OR GABA?)(5A)RECEPTOR?
L31           57 S L30 AND L25-27
L32            1 S VOCAL? AND L25-27
L33            2 S L31 AND PY>1999
L34           55 S L31 NOT L33
L35            5 S L26 OR L27
L36            2 S L34 AND L35
```

476 cites for L24

> cites for named cpds

no cpds related to claimed method

1 cite

55 cites related to GABA receptors

these are the cites in L34 related to the named CPDS in claim 2, titles only

FILE 'USPATFULL' ENTERED AT 14:30:04 ON 06 DEC 2000

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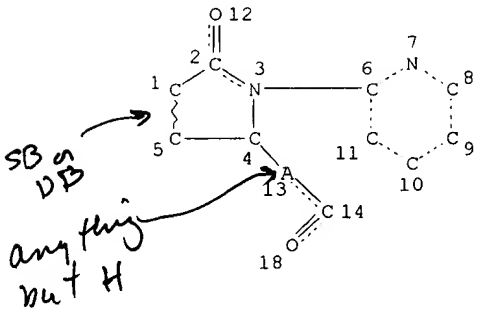
L37           35 S L24
L38            3 S L11
L39            0 S L19
L40       148574 S STAMMER? OR SPEECH? OR STUTTER? OR TALK? OR ?SPEAK?
L41            3 S L40 AND L37-38
L42            3 S L38 AND L40
L43            3 S L41 OR L42
L44            0 S L37 AND VOCAL?
```

3 patents

=> d que 125

L20 302585 SEA FILE=REGISTRY ABB=ON PLU=ON NC4/ESS AND NC5/ESS
L21 260788 SEA FILE=REGISTRY ABB=ON PLU=ON L20 AND O/ELS
L22 STR



NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

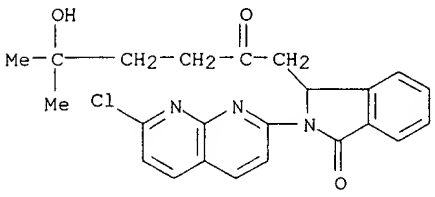
GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 15

STEREO ATTRIBUTES: NONE
L24 477 SEA FILE=REGISTRY SUB=L21 SSS FUL L22
L25 476 SEA FILE=HCAPLUS ABB=ON PLU=ON L24

STRS of the named cpds in CLAIM 2

=> d scan l11

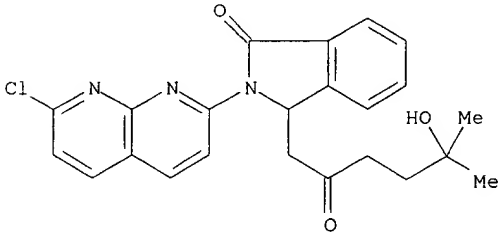
L11 3 ANSWERS REGISTRY COPYRIGHT 2000 ACS
IN **1H-Isoindol-1-one, 2-(7-chloro-1,8-naphthyridin-2-yl)-2,3-dihydro-3-(5-hydroxy-5-methyl-2-oxohexyl)- (9CI)**
MF **C23 H22 Cl N3 O3**



HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):2

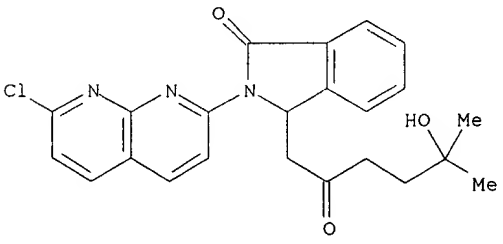
L11 3 ANSWERS REGISTRY COPYRIGHT 2000 ACS
IN **1H-Isoindol-1-one, 2-(7-chloro-1,8-naphthyridin-2-yl)-2,3-dihydro-3-(5-hydroxy-5-methyl-2-oxohexyl)-, (-)- (9CI)**
MF **C23 H22 Cl N3 O3**

Rotation (-).



L11 3 ANSWERS REGISTRY COPYRIGHT 2000 ACS
IN **1H-Isoindol-1-one, 2-(7-chloro-1,8-naphthyridin-2-yl)-2,3-dihydro-3-(5-hydroxy-5-methyl-2-oxohexyl)-, (+)- (9CI)**
MF **C23 H22 Cl N3 O3**

Rotation (+).

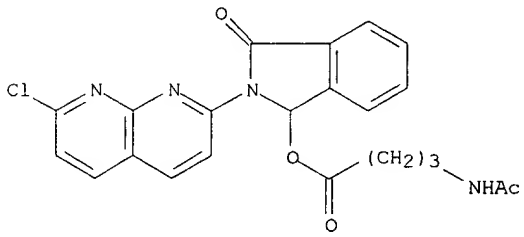


ALL ANSWERS HAVE BEEN SCANNED

=> d scan l19

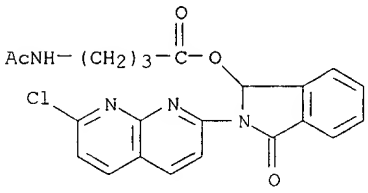
L19 3 ANSWERS REGISTRY COPYRIGHT 2000 ACS
IN **Butanoic acid, 4-(acetylamino)-, 2-(7-chloro-1,8-naphthyridin-2-yl)-2,3-dihydro-3-oxo-1H-isoindol-1-yl ester, (-)- (9CI)**
MF **C22 H19 Cl N4 O4**

Rotation (-).



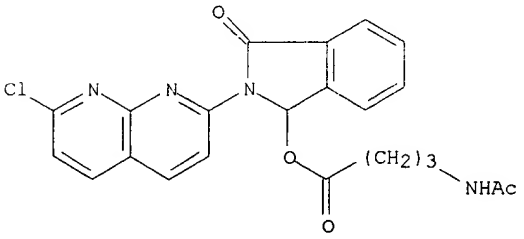
HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):2

L19 3 ANSWERS REGISTRY COPYRIGHT 2000 ACS
IN **Butanoic acid, 4-(acetylamino)-, 2-(7-chloro-1,8-naphthyridin-2-yl)-2,3-dihydro-3-oxo-1H-isoindol-1-yl ester (9CI)**
MF **C22 H19 Cl N4 O4**



L19 3 ANSWERS REGISTRY COPYRIGHT 2000 ACS
IN **Butanoic acid, 4-(acetylamino)-, 2-(7-chloro-1,8-naphthyridin-2-yl)-2,3-dihydro-3-oxo-1H-isoindol-1-yl ester, (+)- (9CI)**
MF **C22 H19 Cl N4 O4**

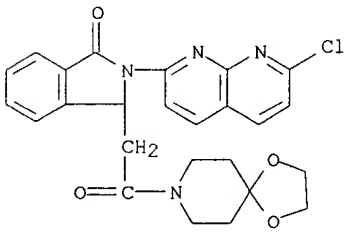
Rotation (+).



ALL ANSWERS HAVE BEEN SCANNED

=> d bib abs hitstr 132

L32 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2000 ACS
AN 1992:228126 HCAPLUS
DN 116:228126
TI Effect of a new anxiolytic, DN-2327, on learning and memory in rats
AU Wada, Takeo; Fukuda, Naohisa
CS Dev. Div., Takeda Chem. Ind. Ltd., Osaka, 532, Japan
SO Pharmacol., Biochem. Behav. (1992), 41(3), 573-9
CODEN: PBBHAU; ISSN: 0091-3057
DT Journal
LA English
AB The effects of a new anxiolytic, DN-2327, on the execution of step-through passive avoidance and delayed spontaneous alternation tasks were assessed and compared with those of diazepam (DZP) and buspirone. DN-2327 and buspirone (both 10 and 20 mg/kg, oral) impaired performance in the 48-h passive avoidance recall test when given prior to the test session, but not when given before the training trial, DZP impaired the performance at doses of more than 5 and more than 10 mg/kg oral when given prior to the test session and when given bvefore the training trial, resp. The actgion of DZP (10 mg/kg, oral) when given before the training trial was antagonized by flumazenil (20 mg/kg, i.p.) and tended to be antagonized by DN-2327 (10 and 30 mg/kg, oral), but was not affected by buspirone. No evidence for possible amnesic effects of DN-2327 or buspirone on working memory was found in the delayed spontaneous alternation task, but DZP (3 and 10 mg/kg, oral) caused impairment of working memory. Electroshock sensitivities detected by flinch, jump, and **vocalization** threhsolds were not influenced by DN-2327 (30 and 100 mg/kg, oral), DZP (10 and 30 mg/kg, oral) or buspirone (30 and 100 mg/kg, oral). These results suggest that although DN-2327 and buspirone have amnesic effects in tasks that involve anxiety they do not impair acquisition or working memory, both of which are impaired by DZP, and that DN-2327 tends to act as an antagonist on the acquisition impairment caused by DZP in the passive avoidance task.
IT **103255-66-9**, DN-2327
RL: BIOL (Biological study)
(learning and memory response to, as anxiolytic)
RN 103255-66-9 HCAPLUS
CN 1,4-Dioxa-8-azaspiro[4.5]decane, 8-[[2-(7-chloro-1,8-naphthyridin-2-yl)-2,3-dihydro-3-oxo-1H-isoindol-1-yl]acetyl]- (9CI) (CA INDEX NAME)

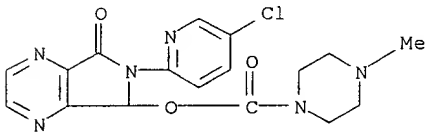


STR

HUI 09/628,803

=> d bib abs hitstr l34 1-55

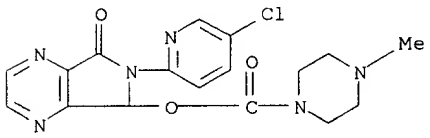
L34 ANSWER 1 OF 55 HCAPLUS COPYRIGHT 2000 ACS
AN 2000:65110 HCAPLUS
DN 132:343144
TI Zaleplon displays a selectivity to recombinant **GABAA receptors** different from zolpidem, zopiclone and benzodiazepines
AU Damgen, Kerstin; Luddens, Hartmut
CS Clinical Research Group, Department of Psychiatry, University of Mainz, Mainz, D-55131, Germany
SO Neurosci. Res. Commun. (1999), 25(3), 139-148
CODEN: NRCOEE; ISSN: 0893-6609
PB Wiley-Liss, Inc.
DT Journal
LA English
AB A chem. heterogeneous group of compds. acts at the benzodiazepine (BZ) recognition site of the **GABAA receptor** complex. Whereas most 1,4-BZs recognize all **GABAA**/BZ **receptors** with similar affinity, other compds. differentiate between the large no. of native **GABAA receptors**, which assemble from the >14 known subunits. This work describes the in vitro binding properties of the BZs lorazepam and Ro 15-4513 plus the 3 hypnotics zaleplon, zolpidem and zopiclone to 8 receptor subtypes. Lorazepam fits well into the general scheme for other 1,4-BZs with respect to its receptor subtype selectivity in spite of its clin. different use. Zaleplon but not zolpidem recognizes .alpha.2- and .alpha.3-receptors that addnl. contain a .beta.j and the .gamma.3-subunit. It is concluded that the hypnotic zaleplon displays a novel receptor selectivity different from that of other BZ receptor ligands in clin. use. The data indicate that the .alpha.1.beta.j.gamma.2 receptor subtype may be the main mediator of the hypnotic properties of BZ receptor ligands.
IT **43200-80-2**, Zopiclone
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(binding of the hypnotics zaleplon, zolpidem, and zopiclone and the benzodiazepines lorazepam and Ro 15-4513 to **GABAA receptor** subtypes)
RN 43200-80-2 HCAPLUS
CN 1-Piperazinecarboxylic acid, 4-methyl-, 6-(5-chloro-2-pyridinyl)-6,7-dihydro-7-oxo-5H-pyrrolo[3,4-b]pyrazin-5-yl ester (9CI) (CA INDEX NAME)



RE.CNT 26
RE
(1) Allen, D; Eur J Clin Pharmacol 1993, V45, P313 HCAPLUS
(3) Cheng, Y; Biochem Pharmacol 1973, V22, P3099 HCAPLUS
(5) Eichinger, A; J Neurochem 1984, V43, P1745 HCAPLUS
(6) Gavish, M; Nature 1980, V287, P651 HCAPLUS
(7) Gluckman, M; J Clin Psychiatry 1978, V39, P3 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L34 ANSWER 2 OF 55 HCAPLUS COPYRIGHT 2000 ACS
AN 1999:676241 HCAPLUS
DN 132:43
TI Sleep and its modulation by drugs that affect **GABAA receptor** function
AU Lancel, Marike; Steiger, Axel
CS Max-Planck-Institut fur Psychiatrie, Munchen, D-80804, Germany
SO Angew. Chem., Int. Ed. (1999), 38(19), 2853-2864
CODEN: ACIEF5; ISSN: 1433-7851
PB Wiley-VCH Verlag GmbH
DT Journal; General Review

LA English
AB A review with numerous refs. Insomnia, defined as a discrepancy between the need for sleep and the perceived quantity and/or quality of sleep, is a major medical problem. The most frequently prescribed sleeping pills are agonistic modulators of **GABAA receptors**. To examine the changes in sleep that can be induced by the stimulation of **GABAA receptor** function, this article reviews the hypnotic properties of the different classes of agonistic modulators of **GABAA receptors**, such as barbiturates, benzodiazepines, zolpidem, zopiclone, and neuroactive steroids, and of selective GABAA agonists assessed in various mammalian species, including noninsomniac subjects. Although quant. differences clearly exist, the agonistic modulators appear to have many actions in common. They are very effective in inducing and maintaining sleep and, with a possible exception of the neurosteroids, inhibit the dream-assocd. rapid eye movement (REM) stage of sleep. With regard to the signals in the EEG during non-REM sleep, all these drugs promote the occurrence of spindles characteristic for shallow sleep and, with the exception of barbiturates, depress slow waves which usually identify deep sleep. Upon chronic usage all these drugs may produce tolerance and dependence. This occurs to the greatest extent with barbiturates and to the least extent with the newer hypnotics zolpidem and zopiclone. The small no. of studies on the GABA analogs and the selective GABAA agonists muscimol and 4,5,6,7-tetrahydroisoxazolopyridin-3-ol (THIP) indicate that these compds. have little effect on sleep initiation, but may increase sleep maintenance and promote deep sleep without disrupting REM sleep. The hypnotic properties of these GABAA agonists seem to differ considerably from those of agonistic modulators and may have beneficial effects in the treatment of disturbances in maintaining sleep and of nonrefreshing sleep.
IT **43200-80-2**, Zopiclone
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(sleep and its pharmacol. modulation by **GABAA receptor** agonists)
RN 43200-80-2 HCAPLUS
CN 1-Piperazinecarboxylic acid, 4-methyl-, 6-(5-chloro-2-pyridinyl)-6,7-dihydro-7-oxo-5H-pyrrolo[3,4-b]pyrazin-5-yl ester (9CI) (CA INDEX NAME)



RE.CNT 168
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(1) Achermann, P; Human Neurobiol 1987, V6, P203 HCAPLUS
(2) Adam, K; Br Med J 1976, V1, P1558 HCAPLUS
(3) Aeschbach, D; Neuropsychopharmacology 1994, V11, P237 HCAPLUS
(5) Ator, N; Eur J Pharmacol 1993, V241, P237 HCAPLUS
(7) Barker, J; Life Sci 1986, V39, P1959 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

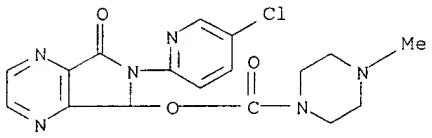
L34 ANSWER 3 OF 55 HCAPLUS COPYRIGHT 2000 ACS
AN 1998:359088 HCAPLUS
DN 129:75730
TI The mechanism of action and pharmacology of zopiclone
AU Karle, Jesper; Nielsen, Mogens
CS The Research Institute of Biological Psychiatry, St Hans Hospital, Roskilde, DK-4000, Den.
SO Rev. Contemp. Pharmacother. (1998), 9(2), 77-87
CODEN: RCPHFW; ISSN: 0954-8602
PB Marius Press
DT Journal; General Review
LA English
AB Development of new hypnotics with fewer unwanted effects has a high priority. The cyclopyrrolone deriv. zopiclone showed potent

sedative-hypnotic properties in humans. Zopiclone is chem. unrelated to the 1,4-benzodiazepines. However, its pharmacol. profile is closely related to that of the 1,4-benzodiazepines. Zopiclone, like benzodiazepines, potentiates the function of .**gamma**.-**aminobutyric acid** (**GABA**) at the **GABAA receptor** complex. Results of various radioligand binding studies indicate that there are subtle differences in the mol. interaction of zopiclone and benzodiazepines with the **GABAA receptor**. Probably, zopiclone interacts with a site which is different from, but closely assocd. with, the benzodiazepine binding site within the **GABAA receptor** complex. The animal behavioral pharmacol. properties of zopiclone are qual. similar to those of the benzodiazepines; zopiclone exerts sedative-hypnotic, anticonvulsant, muscle relaxant, antiaggressive and anticonflict actions in exptl. animals. The sedative-hypnotic, anticonflict and antiaggressive actions are comparable to those of most benzodiazepines, whereas anticonvulsant and muscle relaxant effects seem to be weaker than those induced by benzodiazepines. Zopiclone has a high margin of safety. The short duration of action of zopiclone is favorable for a hypnotic. Based on biochem. and behavioral data, zopiclone may have an advantageous side-effect profile, esp. regarding tolerance/phys. dependence liability. A review with many refs.

IT **43200-80-2**, Zopiclone
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); PEP (Physical, engineering or chemical process); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(mechanism of action and pharmacol. of)

RN 43200-80-2 HCAPLUS

CN 1-Piperazinecarboxylic acid, 4-methyl-, 6-(5-chloro-2-pyridinyl)-6,7-dihydro-7-oxo-5H-pyrrolo[3,4-b]pyrazin-5-yl ester (9CI) (CA INDEX NAME)



L34 ANSWER 4 OF 55 HCAPLUS COPYRIGHT 2000 ACS

AN 1998:275893 HCAPLUS

DN 129:23332

TI Effects of alcohol, zolpidem, and some other sedatives and hypnotics on human performance and memory

AU Mattila, M. J.; Vanakoski, J.; Kalska, H.; Seppala, T.

CS Institute of Biomedicine (Department of Pharmacology and Toxicology) and Department of Applied Psychology, University of Helsinki, Helsinki, Finland

SO Pharmacol., Biochem. Behav. (1998), 59(4), 917-923
CODEN: PBBHAU; ISSN: 0091-3057

PB Elsevier Science Inc.

DT Journal

LA English

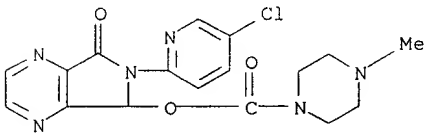
AB Zolpidem (Zol), an .omega.1-agonist, acts via **GABAA receptors** but may differ qual. from diazepam (Dz) and other benzodiazepines (BZDs). We conducted a placebo-controlled, randomized, double-blind, and crossover study to compare the psychomotor and cognitive effects of 15 mg Zol with those of 15 mg Dz, 30 mg oxazepam (Ox), 7.5 mg zopiclone (Zop), and ethanol (EOH; 0.65 + 0.35 g.kg-t) given to 12 subjects at 1-wk intervals. Psychomotor tests (symbol digit substitution,' simulated driving, flicker fusion, body sway) were done before and 1, 3.5, and 5 h after intake; immediate and delayed memory were measured between 1.5 and 3.5 h. The plasma concns. of drugs were measured by gas chromatog. and by radioreceptor assay (RRA). The mean values of EOH in blood at 1.5, 4, and 5.5 h were 0.82, 0.88, and 0.6 g/L-1, and the mean values of RRA-assayed plasma Dz were 470, 330, and 210 .mu.g/L-1, resp. The corresponding values of other hypno-sedatives, in Dz equiv.

(.mu.g/L-1), were 550, 750, and 330 for Ox; 350, 270, and 70 for Zol; and 160, 210, and 70 for Zop. The std. RRA graph for Zol was significantly flatter than those for other hypnotics. Zol impaired coordinative, reactive, and cognitive skills at 1 and 3.5 h more clearly than the other agents did, the most sensitive performance (tracking) still being impaired by Zol at 5 h. Dz and Zop were less active than Zol objectively; subjective sedation after Dz and Zol was stronger than after Zop. Compared to placebo, all active agents tended to impair learning and memory, their decremental effects, in declining order, being Zol, Dz > EOH, Ox > Zop. During the delay, Dz and Zol caused similar losses of material that had been learned. When sepg. "true" delayed memory from immediate memory (attention important), Dz and Zol had equi-effects on delayed memory and were more detrimental than Zop. When contrasting that against the impaired psychomotor performances, it is possible that 15 mg Zol impairs memory relatively less than 15 mg Dz does.

IT **43200-80-2**, Zopiclone
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(alc., zolpidem, and other sedatives and hypnotics effect on human performance and memory)

RN 43200-80-2 HCAPLUS

CN 1-Piperazinecarboxylic acid, 4-methyl-, 6-(5-chloro-2-pyridinyl)-6,7-dihydro-7-oxo-5H-pyrrolo[3,4-b]pyrazin-5-yl ester (9CI) (CA INDEX NAME)



L34 ANSWER 5 OF 55 HCAPLUS COPYRIGHT 2000 ACS

AN 1997:737750 HCAPLUS

DN 128:57332

TI Randomized, double-blind, placebo-controlled trial of the efficacy and tolerability of a new isoindoline derivative (DN-2327) in generalized anxiety

AU Linden, M.; Hadler, D.; Hofmann, S.

CS Department of Psychiatry, Free University of Berlin, Berlin, D14050, Germany

SO Hum. Psychopharmacol. (1997), 12(5), 445-452
CODEN: HUPSEC; ISSN: 0885-6222

PB Wiley

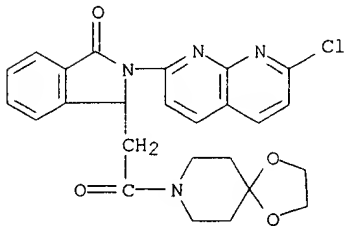
DT Journal

LA English

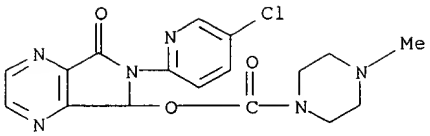
AB Generalized anxiety disorders are frequent, chronic, and disabling illnesses for which so far ideal drug treatment is not available. A new promising anxiolytic drug is DN-2327, a non-benzodiazepine isoindoline deriv., which has shown in animals to have anxiolytic, taming, antiaggressive, and anticonvulsive effects without relevant sedative properties, or signs of dependence. DN-2327 showed a higher affinity for the BZ1-**GABA receptor** in comparison to diazepam or flunitrazepam. DN-2327 is rapidly absorbed with a tmax of 2.4 h, both after single and multiple dosing. A steady state is reached after 2-3 days of treatment. The elimination half-life is about 8 h. A first 4-wk double-blind comparative study between DN-2327 and placebo was conducted in 126 patients suffering from generalized anxiety disorders, and treated as outpatients by general practitioners. The score of the Hamilton Anxiety Scale dropped significantly from baseline to week 1 with further improvement until the final visit after 4 wk. Between-group comparisons are significant from week 1 onward. Similar results were found with the self-rating KUSTA scale. Patients treated with DN-2327 reported more unwanted events, mostly dizziness and tiredness, than patients under placebo.

IT **103255-66-9**, DN-2327
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

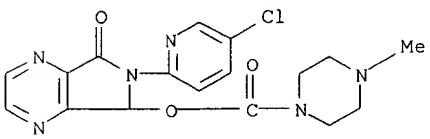
(DN-2327 efficacy and tolerability in humans with generalized anxiety)
RN 103255-66-9 HCAPLUS
CN 1,4-Dioxa-8-azaspiro[4.5]decane, 8-[[2-(7-chloro-1,8-naphthyridin-2-yl)-2,3-dihydro-3-oxo-1H-isoindol-1-yl]acetyl]- (9CI) (CA INDEX NAME)



L34 ANSWER 6 OF 55 HCAPLUS COPYRIGHT 2000 ACS
AN 1997:32775 HCAPLUS
DN 126:84514
TI Failure of long-term administration of zopiclone and zolpidem to induce tolerance in mice
AU Serra, Mariangela; Concas, Alessandra; Biggio, Giovanni
CS Department Experimental Biology, University Cagliari, Cagliari, Italy
SO Neurosci. Res. Commun. (1996), 19(3), 169-178
CODEN: NRCOEE; ISSN: 0893-6609
PB Wiley
DT Journal
LA English
AB The ability of a challenge dose of the cyclopyrrolone zopiclone to antagonize both the convulsions and the increase in t-[35S]butylbicyclophosphorothionate ([35S]TBPS) binding to the **gamma.-aminobutyric acid** type A (**GABAA**) **receptor** elicited by isoniazid, an inhibitor of central GABAergic function, was evaluated in mice subjected to long-term treatment (20 mg/kg, i.p.; three times daily for 30 days) with the drug. The effects of zopiclone were compared with those of the imidazopyridine zolpidem and the benzodiazepine flunitrazepam. The challenge dose of zopiclone (10 and 100 mg/kg, i.p., resp.), administered 36 h after the last injection of the chronic treatment protocol, reduced both isoniazid-induced convulsions and the isoniazid-induced increase in [35S]TBPS binding to the same marked extent as in control mice. Similar results were obtained in mice chronically exposed to zolpidem (15 mg/kg), i.p., whereas mice subjected to long-term treatment with flunitrazepam (1 mg/kg, i.p.) became tolerant to this drug. These results indicate that long-term treatment with zopiclone or zolpidem failed to induce tolerance to the effects of these drugs on **GABAA receptor** function. Consistent with these observations, [35S]TBPS binding was increased (+18 to 28%) 12 and 48 h after, and decreased (-15%) 96 h after, discontinuation of long-term flunitrazepam administration. In contrast, discontinuation of chronic treatment with zopiclone or zolpidem failed to modify this parameter. These data indicate that long-term treatment with the hypnotic zopiclone did not induce discontinuation syndrome in mice sexual behavior.
IT **43200-80-2**, Zopiclone
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tolerance to the effects of hypnotic zopiclone at **GABAA receptor** in comparison with zolpidem and flunitrazepam)
RN 43200-80-2 HCAPLUS
CN 1-Piperazinecarboxylic acid, 4-methyl-, 6-(5-chloro-2-pyridinyl)-6,7-dihydro-7-oxo-5H-pyrrolo[3,4-b]pyrazin-5-yl ester (9CI) (CA INDEX NAME)

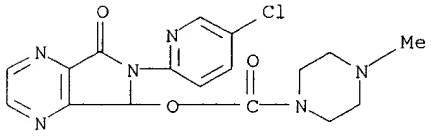


L34 ANSWER 7 OF 55 HCAPLUS COPYRIGHT 2000 ACS
AN 1996:491059 HCAPLUS
DN 125:238265
TI Acute, subchronic and discontinuation effects of zopiclone on sleep EEG and nocturnal melatonin secretion
AU Mann, K.; Bauer, H.; Hiemke, C.; Roeschke, J.; Wetzel, H.; Benkert, O.
CS Department of Psychiatry, University of Mainz, Untere Zahlbacher Strasse 8, Mainz, D-55101, Germany
SO Eur. Neuropsychopharmacol. (1996), 6(3), 163-168
CODEN: EURNE8; ISSN: 0924-977X
DT Journal
LA English
AB Zopiclone is a new short half-life cyclopyrrolone hypnotic agent acting at the **GABA**-benzodiazepine **receptor** complex. To characterize its pharmacol. profile, the effects of 7.5 mg zopiclone on nocturnal melatonin secretion were investigated under polysomnog. control in 11 healthy subjects following acute and subchronic administration as well as after abrupt discontinuation of the drug. No effect of zopiclone on the melatonin plasma levels could be obsd. Regarding both total melatonin prodn. and the temporal pattern of melatonin secretion during the night, there was no difference between placebo baseline condition, acute and subchronic administration, and discontinuation. In contrast, the sleep EEG data demonstrated the hypnotic efficacy of zopiclone under acute administration and indicated a rebound insomnia after abrupt discontinuation. Moreover, alterations of sleep architecture were found under treatment as well as after discontinuation. Whereas, with regard to sleep EEG parameters, zopiclone appears to be comparable with some short-acting benzodiazepines, a discrepancy between the missing effect of zopiclone on pineal function and the suppressing influence of benzodiazepines known from the literature becomes obvious. The fact that zopiclone does not interfere with nocturnal melatonin secretion at pharmacol. active doses as indicated by alterations in sleep EEG parameters might possibly point to a pharmacodynamic difference between the two drug classes.
IT **43200-80-2**, Zopiclone
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(effects of zopiclone on sleep EEG and nocturnal melatonin secretion in humans in relation to **GABA receptor** complex)
RN 43200-80-2 HCAPLUS
CN 1-Piperazinecarboxylic acid, 4-methyl-, 6-(5-chloro-2-pyridinyl)-6,7-dihydro-7-oxo-5H-pyrrolo[3,4-b]pyrazin-5-yl ester (9CI) (CA INDEX NAME)



L34 ANSWER 8 OF 55 HCAPLUS COPYRIGHT 2000 ACS
AN 1996:361401 HCAPLUS
DN 125:104238
TI Affinity of various ligands for **GABAA receptors** containing .alpha.4.beta.3.gamma.2, .alpha.4.gamma.2, or .alpha.1.beta.3.gamma.2 subunits
AU Scholze, Petra; Ebert, Veronika; Sieghart, Werner

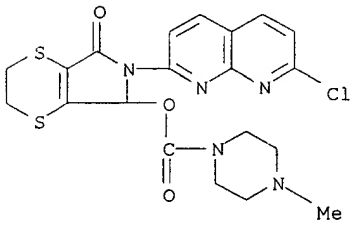
CS Department of Biochemical Psychiatry, University Clinic for Psychiatry, Waehringer Guertel 18-20, 1090, Vienna, Austria
SO Eur. J. Pharmacol. (1996), 304(1-3), 155-162
CODEN: EJPHAZ; ISSN: 0014-2999
DT Journal
LA English
AB The potency of 30 benzodiazepine binding site ligands from 14 different structural classes for inhibition of [3H]Ro 15-4513 (ethyl-8-azido-5,6-dihydro-5-methyl-6-oxo-4H-imidazo[1,5-a][1,4]benzodiaz epine-3-carboxylate) binding to human embryonic kidney (HEK) 293 cells transiently transfected with .alpha.4.beta.3.gamma.2S or .alpha.1.beta.3.gamma.2S subunits of **GABAA receptors** was investigated. Most of these compds. were unable to significantly inhibit [3H]Ro 15-4513 binding to .alpha.4.beta.3.gamma.2S receptors under conditions where they potently inhibited binding to .alpha.1.beta.3.gamma.2S receptors. Nevertheless, compds. from four different structural classes were identified which exhibited a high affinity for .alpha.4.beta.3.gamma.2S receptors. Variation of the structure of these compds. could lead to new ligands selectively interacting with .alpha.4.beta.3.gamma.2S receptors. Compds. interacting with .alpha.4.beta.3.gamma.2S receptors were also able to inhibit [3H]Ro 15-4513 binding to receptors consisting of .alpha.4.gamma.2S subunits with comparable potency. These results support the conclusion that the .alpha. subunit is a major determinant of the benzodiazepine binding site properties of **GABAA receptors** contg. .alpha. and .gamma. subunits.
IT **43200-80-2**, Zopiclone
RL: BPR (Biological process); PRP (Properties); BIOL (Biological study); PROC (Process)
(affinity of various ligands for **GABAA receptors** contg. .alpha.4.beta.3.gamma.2, .alpha.4.gamma.2, or .alpha.1.beta.3.gamma.2 subunits)
RN 43200-80-2 HCAPLUS
CN 1-Piperazinecarboxylic acid, 4-methyl-, 6-(5-chloro-2-pyridinyl)-6,7-dihydro-7-oxo-5H-pyrrolo[3,4-b]pyrazin-5-yl ester (9CI) (CA INDEX NAME)



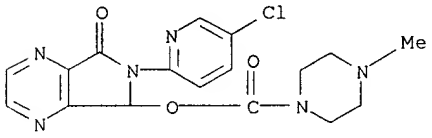
L34 ANSWER 9 OF 55 HCAPLUS COPYRIGHT 2000 ACS
AN 1995:527712 HCAPLUS
DN 122:282113
TI Autoradiographic distribution of [3H]suriclone binding sites in the rat brain
AU Malgouris, Christiane; Perrot, Fabienne; Dupuis, Marion; Kiosseff, Therese; Daniel, Marc; Blanchard, Jean-Charles; Doble, Adam
CS Rhone-Poulenc Rorer, Centre de Recherche de Vitry-Alfortville, Vitry-sur-Seine, Fr.
SO Drug Dev. Res. (1995), 34(4), 336-43
CODEN: DDREDK; ISSN: 0272-4391
DT Journal
LA English
AB Autoradiog. showed that the binding of [3H]suriclone to rat brain sections was displaced completely by 1 .mu.M flumazenil; satn. expts. revealed a single class of binding sites with a KD value of 1.19 nM and a Bmax of 1.05 pmol/mg protein. The pharmacol. specificity of [3H]suriclone binding was close to that of the benzodiazepine (BZ) binding site on the **GABAA receptor**. Unlike the binding of BZ agonists, [3H]suriclone binding to rat brain sections was not increased in the presence of GABA, and unlike imidazopyridines such as alpidem, suriclone was unable to discriminate between the BZ1 and BZ2 phenotype of the **GABAA receptor**. The autoradiog. distribution of [3H]suriclone binding sites in the rat brain was heterogeneous and

relatively similar to that previously described for **GABAA receptors** labeled by BZs; some regions, however, such as certain cortical areas, displayed a different labeling. The highest densities were found in the frontal, occipital, parietal, and cingulate cortices (layers I, II, III, IV), in the mol. layer of the cerebellum, in the superior colliculus and in the hippocampus. Moderate binding densities appeared in numerous areas such as the inferior colliculus, the central gray, the dorsal raphe, and the hypothalamus, whereas the caudate putamen, globus pallidus, and thalamic nuclei displayed a low d. of [3H]suriclone binding sites.

IT **53813-83-5**, Suriclone
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(binding of suriclone to brain receptors)
RN 53813-83-5 HCAPLUS
CN 1-Piperazinecarboxylic acid, 4-methyl-, 6-(7-chloro-1,8-naphthyridin-2-yl)-2,3,6,7-tetrahydro-7-oxo-5H-1,4-dithiino[2,3-c]pyrrol-5-yl ester (9CI) (CA INDEX NAME)



IT **43200-80-2**, Zopiclone
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(suriclone binding to brain receptors inhibition by)
RN 43200-80-2 HCAPLUS
CN 1-Piperazinecarboxylic acid, 4-methyl-, 6-(5-chloro-2-pyridinyl)-6,7-dihydro-7-oxo-5H-pyrrolo[3,4-b]pyrazin-5-yl ester (9CI) (CA INDEX NAME)

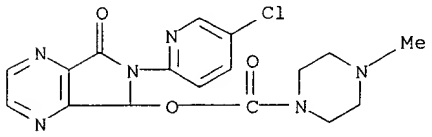


L34 ANSWER 10 OF 55 HCAPLUS COPYRIGHT 2000 ACS
AN 1995:521047 HCAPLUS
DN 122:305875
TI Characterization of novel ligands for wild-type and natural mutant diazepam-insensitive benzodiazepine receptors
AU Wong, Garry; Uusi-Oukari, Mikko; Hansen, Holger C.; Suzdak, Peter D.; Korpi, Esa R.
CS Biomedical Research Center, Alko Group Ltd, P.O. Box 350, FIN-00101, Helsinki, Finland
SO Eur. J. Pharmacol., Mol. Pharmacol. Sect. (1995), 289(2), 335-42
CODEN: EJPPET; ISSN: 0922-4106
DT Journal
LA English
AB A series of benzodiazepine receptor ligands with different chem. structures were evaluated for their affinities at diazepam-sensitive and diazepam-insensitive binding sites for [3H]Ro 15-4513 (ethyl-8-azido-5,6-dihydro-5-methyl-6-oxo-4H-imidazo-[1,5a][1,4]benzodiazepine-3-carboxylate) in cerebellar **GABAA receptors**. Rats of Wistar strain and of alc.-sensitive (ANT) and alc.-insensitive (AT) lines were used. The ANT rats possess a single point mutation in their **GABAA receptor** .alpha.6 subunit, which makes

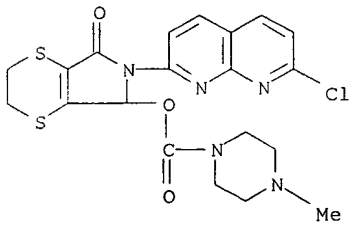
their diazepam-insensitive sites sensitive to benzodiazepine agonists, unlike those of AT and Wistar rats. All compds. evaluated displayed high-affinity binding to diazepam-sensitive sites (Ki<50 nM). In contrast, a wider range of affinities were obsd. at diazepam-insensitive sites which depended upon the basic structure and substitutions. The 7- and 8-halogen substituted imidazobenzodiazepines and 12-halogen substituted diimidazoquinazolines displayed the highest affinities (Ki<15 nM), while intermediate to low affinities (100<Ki<4000 nM) were displayed by imidazoquinazolines, thienopyrimidines, one oxoimidazoquinoxaline, and some cyclopyrrolones. The imidazoquinoxalines evaluated displayed the lowest affinity (Ki>10000 nM). The oxoimidazoquinoxaline, 6-chloro-3-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-4,5-dihydro-5-isopropyl-4-o xo-imidazo[1,5-a]quinoxaline (NNC 14-0578) and suriclone represent the first benzodiazepine receptor full agonists to bind with relatively high affinity (Ki.apprx.100 nM) to diazepam-insensitive sites. The 5-position substituted methoxybenzyl, dimethylallyl, and 4-fluorobenzyl oxoimidazoquinoxaline analogs demonstrated a 58-336-fold higher affinity for ANT than AT diazepam-insensitive sites. Classical benzodiazepines having a 5-Ph substituent have demonstrated a similar preference for ANT sites, suggesting that all these structures bind to diazepam-insensitive sites in the same orientation. The other compds. evaluated demonstrated only a more modest selectivity (1-12-fold), indicating different structural requirements for binding to mutant ANT and wild-type AT and Wistar receptors. These results expand the range of ligands which display high affinity for diazepam-insensitive sites. Such compds. should be helpful in detg. intrinsic actions of high-affinity ligands at these sites and in assessing the contribution of these sites in enhanced sedative sensitivity of cerebellar function in the ANT rats.

IT **43200-80-2**, Zopiclone **53813-83-5**, Suriclone
117705-18-7, RP 60503 **133737-48-1**, RP 59037
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); PRP (Properties); BIOL (Biological study); PROC (Process)
(characterization of novel ligands for wild-type and natural mutant diazepam-insensitive benzodiazepine receptors)

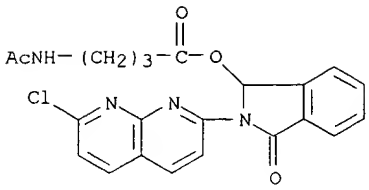
RN 43200-80-2 HCAPLUS
CN 1-Piperazinecarboxylic acid, 4-methyl-, 6-(5-chloro-2-pyridinyl)-6,7-dihydro-7-oxo-5H-pyrrolo[3,4-b]pyrazin-5-yl ester (9CI) (CA INDEX NAME)



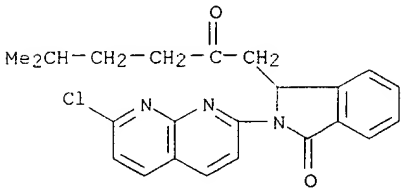
RN 53813-83-5 HCAPLUS
CN 1-Piperazinecarboxylic acid, 4-methyl-, 6-(7-chloro-1,8-naphthyridin-2-yl)-2,3,6,7-tetrahydro-7-oxo-5H-1,4-dithiino[2,3-c]pyrrol-5-yl ester (9CI) (CA INDEX NAME)



RN 117705-18-7 HCAPLUS
CN Butanoic acid, 4-(acetylamino)-, 2-(7-chloro-1,8-naphthyridin-2-yl)-2,3-dihydro-3-oxo-1H-isoindol-1-yl ester (9CI) (CA INDEX NAME)



RN 133737-48-1 HCAPLUS
CN 1H-Isoindol-1-one, 2-(7-chloro-1,8-naphthyridin-2-yl)-2,3-dihydro-3-(5-methyl-2-oxohexyl)- (9CI) (CA INDEX NAME)

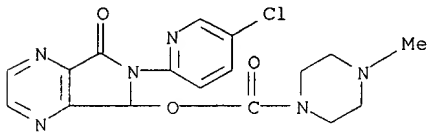


L34 ANSWER 11 OF 55 HCAPLUS COPYRIGHT 2000 ACS
AN 1995:225748 HCAPLUS
DN 122:942
TI The effect of cyclopyrrolones on **GABAA receptor** function is different from that of benzodiazepines
AU Concas, A.; Serra, M.; Santoro, G.; Maciocco, E.; Cuccheddu, T.; Biggio, G.
CS Dep. Experimental Biology, Univ. Cagliari, Cagliari, I-09123, Italy
SO Naunyn-Schmiedeberg's Arch. Pharmacol. (1994), 350(3), 294-300
CODEN: NSAPCC; ISSN: 0028-1298
DT Journal
LA English
AB The effects of the cyclopyrrolones zopiclone and suriclone on the function of the central .gamma.-amino-butyric acid type A (**GABAA**) **receptor** complex in mouse brain were evaluated both in vitro and in vivo. Added in vitro to mouse cerebral cortical membranes, these compds. potently inhibited [3H]flumazenil binding with IC50 (50% inhibitory concn.) values of 35.8 mM (zopiclone) and 1.1 nM (suriclone). Similar results were obtained with cerebellar membranes, indicating that these drugs do not discriminate between putative type I and type II benzodiazepine receptors. The interaction of cyclopyrrolones with recognition sites present at the level of the **GABA receptor** complex appears to be competitive, because zopiclone decreased the affinity to be competitive, because zopiclone decreased the affinity of the receptors for [3H]flumazenil without affecting the maximal no. of binding sites. Moreover, zopiclone and suriclone did not affect the rate of dissocn. of [3H]flumazenil from benzodiazepine receptors. The in vitro efficacy of zopiclone appeared different from that of suriclone and the benzodiazepines diazepam and flunitrazepam. Thus, zopiclone failed to affect muscimol-stimulated 36Cl- untake and only slightly inhibited t-[35S]butylbicyclophosphorothionate ([35S]TBPS) binding. In contrast, like diazepam and flunitrazepam, suriclone increased muscimol-stimulated 36Cl- uptake and markedly inhibited [35S]TBPS binding. On the other hand, suriclone, like zopiclone, did not modify [3H]muscimol binding to mouse cerebral cortical membranes. Moreover, zopiclone antagonized the redn. in [35S]TBPS binding elicited by the benzodiazepine receptor full agonist diazepam. Consistent with its low efficacy in vitro, oral administration of zopiclone (2.5 to 100 mg/kg, p.o.) in mice failed to modify [35S]TBPS binding subsequently measured in cerebral cortical membranes "ex vivo". In contrast, suriclone (10 to 20 mg/kg, p.o.), like diazepam, decreased [35S]TBPS binding measured ex vivo. Moreover, both zopiclone (50 to 100 mg/kg, p.o.) and suriclone (1 to 10 mg/kg, p.o.) abolished the increase in [35S]TBPS binding induced by isoniazid (200 mg/kg, s.c.). These results suggest that suriclone may

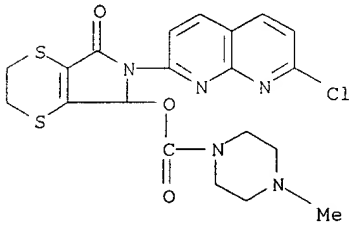
enhance GABAergic transmission with an efficacy similar to that of diazepam. In contrast, the low efficacy of zopiclone both in vitro and in vivo suggests that this drug may act as a partial agonist at benzodiazepine receptors.

IT **43200-80-2**, Zopiclone **53813-83-5**, Suriclone
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(effects of cyclopyrrolones on **GABAA receptor** function are different from those of benzodiazepines)

RN 43200-80-2 HCAPLUS
CN 1-Piperazinecarboxylic acid, 4-methyl-, 6-(5-chloro-2-pyridinyl)-6,7-dihydro-7-oxo-5H-pyrrolo[3,4-b]pyrazin-5-yl ester (9CI) (CA INDEX NAME)



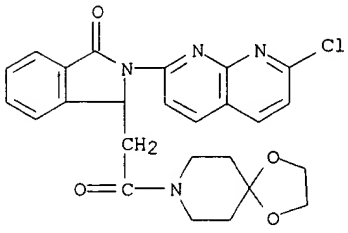
RN 53813-83-5 HCAPLUS
CN 1-Piperazinecarboxylic acid, 4-methyl-, 6-(7-chloro-1,8-naphthyridin-2-yl)-2,3,6,7-tetrahydro-7-oxo-5H-1,4-dithiino[2,3-c]pyrrol-5-yl ester (9CI) (CA INDEX NAME)



L34 ANSWER 12 OF 55 HCAPLUS COPYRIGHT 2000 ACS
AN 1994:261192 HCAPLUS
DN 120:261192
TI Association and agonistic action of DN-2327, a novel isoindoline derivative, on **GABAB receptor** in brain
AU Ichida, Tatsuya; Hirouchi, Masaaki; Mizutani, Hiroshi; Narihara, Rika; Kuriyama, Kinya
CS Dep. Pharmacol., Kyoto Prefect. Univ. Med., Kyoto, 602, Japan
SO Eur. J. Pharmacol., Mol. Pharmacol. Sect. (1994), 267(1), 43-7
CODEN: EJPPET; ISSN: 0922-4106
DT Journal
LA English
AB The assocn. and action of DN-2327, 2-(7-chloro-1,8-naphthyridin-2-yl)-3-[(1,4-dioxa-8-azaspiro[4,5]dec-8-yl)carbonylmethyl]isoindolin-1-one, on the .**gamma**.-**aminobutyric acid** (**GABA**)B **receptor** in rat brain have been examd. DN-2327 inhibited the binding of [3H]**GABA** to **GABAB receptor** in crude synaptic membrane obtained from rat brain. The Scatchard anal. of [3H]**GABA** binding to **GABAB receptor** indicated that DN-2327 induced the decrease in affinity of both high and low affinity binding sites without changing the Bmax values. The forskolin-stimulated adenylate cyclase activity in slices from rat cerebral cortex was significantly suppressed by the addn. of DN-2327. Furthermore, this inhibition by DN-2327 was eliminated by the simultaneous addns. of 2-hydroxy saclofen or CGP 55845A, **GABAB receptor** antagonists. These results suggest that DN-2327 may have not only a high assocn. with **GABAB receptor** but also an agonistic action on the receptor.

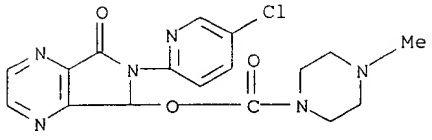
IT **103255-66-9**, DN-2327

RL: BIOL (Biological study)
(as **GABAB receptor** agonist, in brain)
RN 103255-66-9 HCAPLUS
CN 1,4-Dioxa-8-azaspiro[4.5]decane, 8-[[2-(7-chloro-1,8-naphthyridin-2-yl)-2,3-dihydro-3-oxo-1H-isoindol-1-yl]acetyl]- (9CI) (CA INDEX NAME)

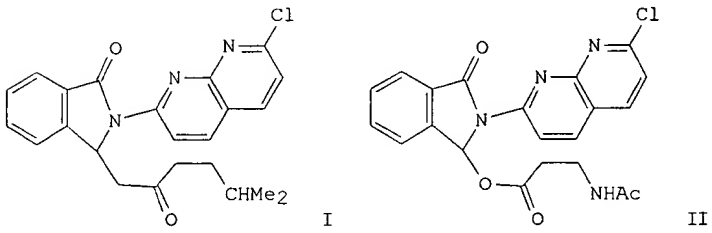


L34 ANSWER 13 OF 55 HCAPLUS COPYRIGHT 2000 ACS
AN 1994:95439 HCAPLUS
DN 120:95439
TI Potentiation of .gamma.-aminobutyric acid-induced chloride currents by various benzodiazepine site agonists with the .alpha.1.gamma.2, .beta.2.gamma.2 and .alpha.1.beta.2.gamma.2 subtypes of cloned .**gamma.-aminobutyric acid** type A **receptors**
AU Im, Haesook K.; Im, Wha Bin; Hamilton, Beverly J.; Carter, Donald B.; VonVoigtlander, Philip F.
CS Upjohn Co., Kalamazoo, MI, 49001, USA
SO Mol. Pharmacol. (1993), 44(4), 866-70
CODEN: MOPMA3; ISSN: 0026-895X
DT Journal
LA English
AB Previous studies with cloned .**gamma.-aminobutyric acid** type A **receptors** expressed in human embryonic kidney cells have indicated that the .alpha.1.beta.2.gamma.2 and .alpha.1.gamma.2 (but not .alpha.1.beta.2) subtypes have benzodiazepine sites. The authors found in this study that even the .beta.2.gamma.2 subtype displays .gamma.-aminobutyric acid-induced Cl- currents that are potentiated by triazolam (a triazolobenzodiazepine). The maximal efficacy of the drug among the subtypes was highest with the .alpha.1.beta.2.gamma.2 subtype, followed by the .alpha.1.gamma.2 and .beta.2.gamma.2 subtypes. These observations led the authors to compare the ability of several benzodiazepine site agonists of diverse chem. structures to potentiate Cl- currents with these subtypes. With the .alpha.1.gamma.2 subtype, diazepam, alpidem, zolpidem, Cl-218872, zopiclone, U-79098 (an imidazoquinoxaline deriv.), and U-90167 (a diimidazoquinazoline deriv.) at 5 .mu.M potentiated Cl- currents to essentially similar levels (slightly lower for a few ligands), compared with those with the .alpha.1.beta.2.gamma.2 subtype. With the .beta.2.gamma.2 subtype, the type 1 ligands zolpidem, alpidem, and Cl-218872 showed no or very low levels of potentiation, whereas less selective ligands such as diazepam, zopiclone, U-78098, and U-90167 displayed levels of Cl- current potentiation comparable to those obsd. with the subtypes contg. the .alpha.1 and .gamma.2 subunits. These data indicate that, in the presence of .gamma.2, .beta.2 may substitute for .alpha.1 in forming the benzodiazepine site of limited sensitivity to the type 1 ligands. It appears that individual ligands for benzodiazepine sites have their own sets of interacting domains, which are distributed in .alpha.1 and .gamma.2, and the agonists activity of type 1 ligands may be more dependent on the .alpha.1-specific domains than is that of less selective ligands.
IT **43200-80-2**, Zopiclone
RL: BIOL (Biological study)
(**GABAA receptor** benzodiazepine site binding by, specificity of)
RN 43200-80-2 HCAPLUS
CN 1-Piperazinecarboxylic acid, 4-methyl-, 6-(5-chloro-2-pyridinyl)-6,7-

dihydro-7-oxo-5H-pyrrolo[3,4-b]pyrazin-5-yl ester (9CI) (CA INDEX NAME)



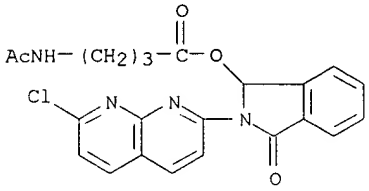
L34 ANSWER 14 OF 55 HCAPLUS COPYRIGHT 2000 ACS
AN 1994:23373 HCAPLUS
DN 120:23373
TI RP 59037 and RP 60503: Anxiolytic cyclopyrrolone derivatives with low sedative potential. Interaction with the .gamma.-aminobutyric acidA/benzodiazepine receptor complex and behavioral effects in the rodent
AU Doble, A.; Canton, T.; Dreisler, S.; Piot, O.; Boireau, A.; Stutzmann, J. M.; Bardone, M. C.; Rataud, J.; Roux, M.; et al.
CS Cent. Rech. Vitry-Alfortville, Rhone-Poulenc Rorer, Vitry-sur-Seine, 94403, Fr.
SO J. Pharmacol. Exp. Ther. (1993), 266(3), 1213-26
CODEN: JPETAB; ISSN: 0022-3565
DT Journal
LA English
GI



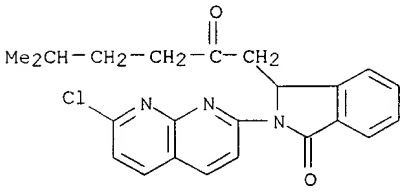
I II

AB This study describes the pharmacol. properties of two novel cyclopyrrolone derivs., RP 59037 (I) and RP 60503 (II), in the rodent. These compds. possess high affinity for the benzodiazepine binding site on the .gamma.-aminobutyric acidA receptor in rat cerebrocortical membranes with Ki values of 0.98 nM (I) and 1.16 nM (II). Neither compd. discriminates between the putative benzodiazepine BZ1 and BZ2 binding site subtypes present in the rat cerebellum and hippocampus, resp. Both compds. protect mice against pentylenetetrazole-induced seizures with ID50 values of 0.21 mg.cntdot.kg-1 oral (I) and 5.96 mg.cntdot.kg-1 oral (II). The two compds. displayed a restricted anticonvulsant profile compared to diazepam and, in this respect, resembled the pyrazoloquinoline partial agonist, CGS 9896. I and II were active in two rat models predictive of anxiolytic drug action, a modified Geller-Seifter conflict paradigm (minimal effect dose, 0.33 mg.cntdot.kg-1 oral for I and 5 mg.cntdot.kg-1 oral for II and the elevated plus maze (minimal ED, 0.33 mg.cntdot.kg-1 oral for I and 5 mg.cntdot.kg-1 oral for II). Only very low activities were obsd. in tests of sedative or myorelaxant effects (EC50 > 50 mg.cntdot.kg-1 oral). It is concluded that the two cyclopyrrolones possess a dissocd. behavioral profile, displaying potent anxiolytic and anticonvulsant properties with little or no sedative or myorelaxant effects. Although both compds. appear to be partial agonists at their allosteric recognition site on the .gamma.-aminobutyric acidA receptor, II seems to be more dissocd. than I, which would be compatible with it having lower intrinsic activity. This difference is reflected in a higher receptor occupancy requirement for activity, and a smaller modulatory effect on the binding of t-[35S]butylbicyclophosphothionate.

IT **117705-18-7**, RP 60503 **133737-48-1**, RP 59037
RL: BIOL (Biological study)
(as anxiolytic with low sedative potential, interaction with **GABAasea**/benzodiazepine **receptor** complex, behavioral response to)
RN 117705-18-7 HCAPLUS
CN Butanoic acid, 4-(acetylamino)-, 2-(7-chloro-1,8-naphthyridin-2-yl)-2,3-dihydro-3-oxo-1H-isoindol-1-yl ester (9CI) (CA INDEX NAME)

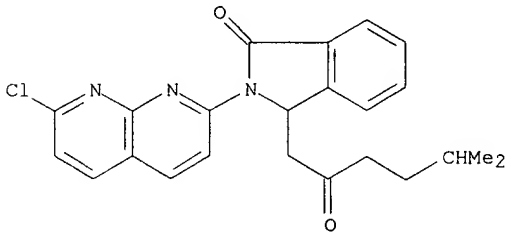


RN 133737-48-1 HCAPLUS
CN 1H-Isoindol-1-one, 2-(7-chloro-1,8-naphthyridin-2-yl)-2,3-dihydro-3-(5-methyl-2-oxohexyl)- (9CI) (CA INDEX NAME)



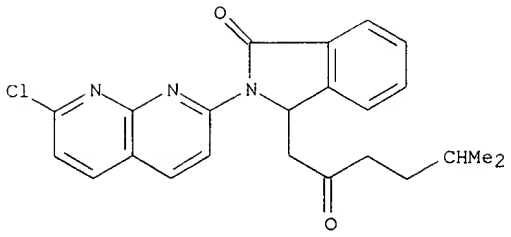
IT **133737-31-2 133737-32-3**, (+)-RP 59037
133737-33-4, (-)-RP 59037 **151602-19-6**, (+)-RP 60503
151602-20-9, (-)-RP 60503 **151602-21-0**
RL: BIOL (Biological study)
(interaction with **GABAA**/benzodiazepine **receptor**, in cerebral cortex membranes, as anxiolytic)
RN 133737-31-2 HCAPLUS
RN 133737-32-3 HCAPLUS
CN 1H-Isoindol-1-one, 2-(7-chloro-1,8-naphthyridin-2-yl)-2,3-dihydro-3-(5-methyl-2-oxohexyl)-, (+)- (9CI) (CA INDEX NAME)

Rotation (+).



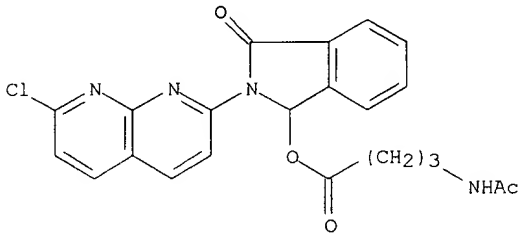
RN 133737-33-4 HCAPLUS
CN 1H-Isoindol-1-one, 2-(7-chloro-1,8-naphthyridin-2-yl)-2,3-dihydro-3-(5-methyl-2-oxohexyl)-, (-)- (9CI) (CA INDEX NAME)

Rotation (-).



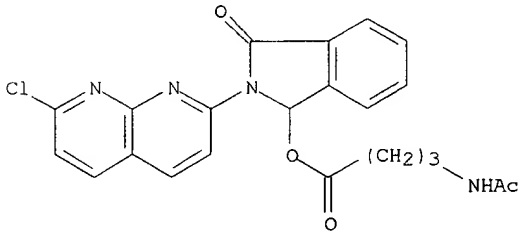
RN 151602-19-6 HCAPLUS
CN Butanoic acid, 4-(acetylamino)-, 2-(7-chloro-1,8-naphthyridin-2-yl)-2,3-dihydro-3-oxo-1H-isoindol-1-yl ester, (+)- (9CI) (CA INDEX NAME)

Rotation (+).



RN 151602-20-9 HCAPLUS
CN Butanoic acid, 4-(acetylamino)-, 2-(7-chloro-1,8-naphthyridin-2-yl)-2,3-dihydro-3-oxo-1H-isoindol-1-yl ester, (-)- (9CI) (CA INDEX NAME)

Rotation (-).



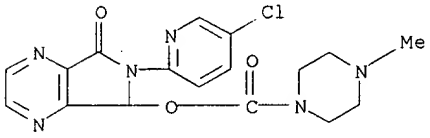
RN 151602-21-0 HCAPLUS

L34 ANSWER 15 OF 55 HCAPLUS COPYRIGHT 2000 ACS
AN 1993:641810 HCAPLUS
DN 119:241810
TI Expression and properties of recombinant .alpha.1.beta.2.gamma.2 and .alpha.5.beta.2.gamma.2 forms of the rat **GABAA receptor**
AU Faure-Halley, C.; Graham, D.; Arbilla, S.; Langer, S. Z.
CS Dep. Biol., Synthelabo Rech., Bagneux, F-92225, Fr.
SO Eur. J. Pharmacol., Mol. Pharmacol. Sect. (1993), 246(3), 283-7
CODEN: EJPPET; ISSN: 0922-4106
DT Journal
LA English
AB The interaction of .omega. (benzodiazepine) modulatory drugs with transiently expressed .alpha.1.beta.2.gamma.2 and .alpha.5.beta.2.gamma.2 forms of the rat **GABAA receptor** was investigated using [3H]flumazenil as a probe in in vitro radioligand binding assays. The imidazopyridines alpidem and zolpidem exhibited pronounced selectivity for the .alpha.1- compared to the .alpha.5-contg. construct, whereas .omega. (benzodiazepine) site modulatory compds. from other chem. series including diazepam, tetrazepam, zopiclone, triazolam, bretazenil and midazolam

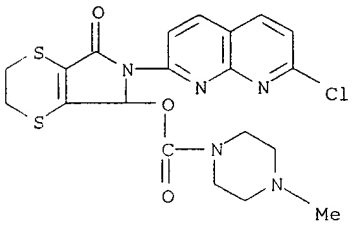
behaved as relatively non-selective drugs. In the presence of 10 .mu.M .gamma.-aminobutyric acid (GABA) the potencies of diazepam, flunitrazepam and midazolam to inhibit [3H]flumazenil binding to the .alpha.1-construct were increased 3 to 5 fold, whereas the 6,7-dimethoxy-4-ethyl-.beta.-carboline-3-carboxylate Me ester a 2.5-fold redn. in potency was obsd. Similar modulatory effects of GABA were obtained with these drugs, using the .alpha.5-construct. The authors suggest that these GABA shift detns. of [3H]flumazenil binding can be used as a rapid test to evaluate the intrinsic activities of .omega. modulatory compds.

IT **43200-80-2**, Zopiclone **53813-83-5**, Suriclone
RL: BIOL (Biological study)
(GABAergicA .alpha.1.beta.2.gamma.2 and .alpha.5.beta.2.gamma.2 recombinant receptor subtypes binding affinity for)

RN 43200-80-2 HCAPLUS
CN 1-Piperazinecarboxylic acid, 4-methyl-, 6-(5-chloro-2-pyridinyl)-6,7-dihydro-7-oxo-5H-pyrrolo[3,4-b]pyrazin-5-yl ester (9CI) (CA INDEX NAME)



RN 53813-83-5 HCAPLUS
CN 1-Piperazinecarboxylic acid, 4-methyl-, 6-(7-chloro-1,8-naphthyridin-2-yl)-2,3,6,7-tetrahydro-7-oxo-5H-1,4-dithiino[2,3-c]pyrrol-5-yl ester (9CI) (CA INDEX NAME)

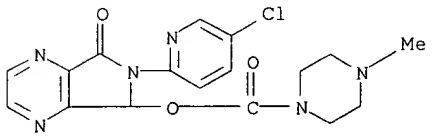


L34 ANSWER 16 OF 55 HCAPLUS COPYRIGHT 2000 ACS
AN 1993:508926 HCAPLUS
DN 119:108926
TI Discriminative stimulus effects of .omega. (BZ) receptor ligands: correlation with in vivo inhibition of [3H]-flumazenil binding in different regions of the rat central nervous system
AU Sanger, D. J.; Benavides, J.
CS Synthelabo Rech., Bagneux, F-92220, Fr.
SO Psychopharmacology (Berlin) (1993), 111(3), 315-22
CODEN: PSCHDL; ISSN: 0033-3158
DT Journal
LA English
AB Rats can be trained to discriminate benzodiazepines (BZ) from vehicle and there is considerable evidence that the stimulus effects of these drugs are mediated by activity at .omega. (BZ) modulatory sites of the **GABAA receptor** complex. A no. of recent studies, however, have indicated that differences may exist between the discriminative stimulus effects of benzodiazepines and those of certain non-benzodiazepine ligands for the .omega. (BZ) receptors (e.g. zolpidem, abecarnil). As it is known that several subtypes of .omega. (BZ) sites are found in the central nervous system, and that drugs such as zolpidem have selectivity for certain subtypes, it is possible that differential stimulus effects may be assocd. with receptor selectivity. In the present study, correlations were calcd. between the potencies of nine compds. with affinity for .omega. receptors (diazepam, lorazepam, triazolam,

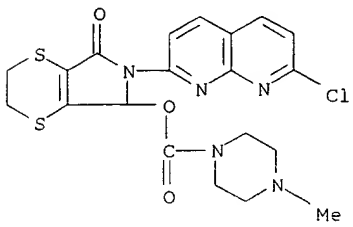
clonazepam, alprazolam, zopiclone, suriclone, CL 218,872 and zolpidem) to substitute for chlordiazepoxide in rats trained to discriminate a dose (5 mg/kg) of this benzodiazepine and the ability of the same compds. to inhibit the binding of [3H]flumazenil from different structures in the rat central nervous system in vivo. The correlations obtained were: cerebellum 0.46, cortex 0.39, striatum 0.78, hippocampus 0.79 and spinal cord 0.95. These different structures are known to contain different relative concns. of .omega.1 (BZ1) and .omega.2 (BZ2) sites with the spinal cord contg. the greatest (80%) and cerebellum the lowest (5%) concn. of .omega.2 (BZ2) sites. Good correlations were also obsd. between the ability of these compds. to substitute for chlordiazepoxide and their potency to inhibit (3H)-flumazenil binding in both cerebellar and spinal cord membranes in vitro indicating that the physiol. relevance of .omega. receptor subtypes cannot be deduced from in vitro studies. The present results are consistent with the possibility that the discriminative stimulus produced by chlordiazepoxide is mediated by activity of .omega.2 (BZ2) sites. No correlations were obsd. between inhibition of [3H]-flumazenil binding and response rate decreases, suggesting that the mechanism underlying this behavioral effect is different from that mediating the discriminative stimulus.

IT **43200-80-2**, Zopiclone **53813-83-5**, Suriclone
RL: PRP (Properties)
(discriminative stimulus effects of, benzodiazepine receptors .omega.1 and .omega.2 specificity comparison for)

RN 43200-80-2 HCAPLUS
CN 1-Piperazinecarboxylic acid, 4-methyl-, 6-(5-chloro-2-pyridinyl)-6,7-dihydro-7-oxo-5H-pyrrolo[3,4-b]pyrazin-5-yl ester (9CI) (CA INDEX NAME)



RN 53813-83-5 HCAPLUS
CN 1-Piperazinecarboxylic acid, 4-methyl-, 6-(7-chloro-1,8-naphthyridin-2-yl)-2,3,6,7-tetrahydro-7-oxo-5H-1,4-dithiino[2,3-c]pyrrol-5-yl ester (9CI) (CA INDEX NAME)



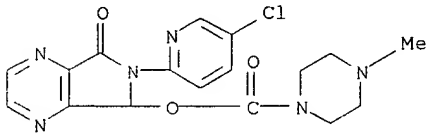
L34 ANSWER 17 OF 55 HCAPLUS COPYRIGHT 2000 ACS
AN 1993:400759 HCAPLUS
DN 119:759
TI Pharmacological properties and mechanism of action of the cyclopyrrolones
AU Stutzmann, J. M.; Piot, O.; Reibaud, M.; Doble, A.; Blanchard, J. C.
CS Biol. Dep., Rhone Poulenc Rorer, Vitry-sur-Seine, 94403, Fr.
SO Encephale (1992), 18(4), 393-400
CODEN: ENCEAN; ISSN: 0013-7006
DT Journal
LA English
AB We present the pharmacol. properties of two cyclopyrrolones, P. as a hypnotic and suriclone as an anxiolytic, and examine their mechanism of action. The effects of zopiclone on the amt. of time spent at each vigilance level have been studied in freely moving rats. Zopiclone from

2.5 mg/kg i.p. extends the duration of slow wave sleep (SWS), concomitantly shortening the periods awake. This SWS inducing effect of zopiclone was more potent after 10 mg/kg i.p.; moreover, zopiclone did not depress REM sleep and no rebound of activity in wakefulness or REM sleep were obsd. the day after zopiclone treatment. In rats, at the cortical level, zopiclone increases the spectral energy in the delta band (0.5 to 4 Hz). This rise in energy appears at doses starting from 1.25 mg/kg p.o. and can also reach the fast frequencies (beta band: 12 to 16 Hz). This power spectrum is characteristic of a compd. having tranquilizing-hypnotic potential. Taken together these EEG results corroborate the clin. studies. In man, zopiclone increased SWS, decreased SWS latency and respected sleep architecture in both healthy volunteers and insomniacs. This respect of sleep structure and the relative short duration of action of zopiclone minimized the residual effects seen upon waking (drowsiness, impairment of psychomotor performance). In the Geller-Seifter test, an operant conflict procedure, the minimal ED (MED) of suriclone in reversing the conflict-induced inhibition of drinking behavior was 2.5 mg.kg-1 p.o. in rats. Depression of unpunished responding is only seen at higher doses (20 mg.kg-1 p.o.). The anxiolytic activity of suriclone has also been demonstrated using the elevated plus-maze test in mice and rats, another std. test for evaluating anxiolytic drugs which does not involve training of the animals. Suriclone increased both the amt. of time spent on the open arms and the no. of entries onto the open arms both p.o. and s.c. In mice (MED = 0.5 mg.kg-1 p.o. and 0.16 mg.kg-1 s.c.) and in rats (MED = 1.25 mg.kg-1 p.o.). Suriclone has shown a proven efficacy in patients with generalized anxiety disorders from 0.1 mg. Although it displayed considerable anxiolytic activity, suriclone appeared to have fewer central depressant effects in muscle relaxant tests, such as the inclined screen test in rats, the grasping test or the loss of righting reflex in mice. Thus in clin. practice, one can hypothesize that the use of suriclone in the treatment of anxiety may be assocd. with few side-effects including little effect on diurnal vigilance. In mice, chronic treatment with some benzodiazepines (4 times daily for 3 days), followed by 2 days withdrawal, leads to the appearance of convulsions after administration of 40 mg/kg i.p. of the partial inverse agonist FG 7142 (N-methyl-.beta. carboline carboxamide), a dose which is normally devoid of convulsant activity. In contrast, no convulsions were obsd. after chronic exposure to cyclopyrrolones, zopiclone and suriclone, even up to 400 mg/kg i.p. daily. These results were confirmed after a ten day treatment period and indicate that cyclopyrrolones do not enhance sensitivity to the partial inverse agonist FG 7142, which could suggest that these compds. do not induce phys. dependence. Anxiolytic-hypnotic drugs could modify in an allosteric manner the conformation of the **GABA receptor**-complex such that it becomes more sensitive to its neuromediator. Biochem. studies strongly suggest that cyclopyrrolones interact on an alternative binding domain to benzodiazepines or at least in a different way within the heterogeneous **GABA receptor** complex. Studies with the cyclopyrrolones confirm the importance of GABA function in the regulation of sleep and of anxiety. Zopiclone (Imovane.RTM.) and suriclone (Suri.RTM.) belong to this new chem. family and resp. possess potent hypnotic and anxiolytic activities in exptl. and clin. pharmacol.

IT **43200-80-2**, Zopiclone
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmacol. of, as cyclopyrrolone and hypnotic)

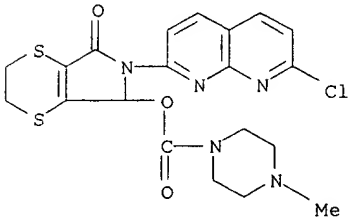
RN 43200-80-2 HCAPLUS

CN 1-Piperazinecarboxylic acid, 4-methyl-, 6-(5-chloro-2-pyridinyl)-6,7-dihydro-7-oxo-5H-pyrrolo[3,4-b]pyrazin-5-yl ester (9CI) (CA INDEX NAME)

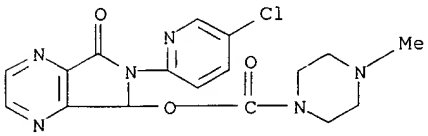


IT **53813-83-5**, Suriclone
RL: BAC (Biological activity or effector, except adverse); THU

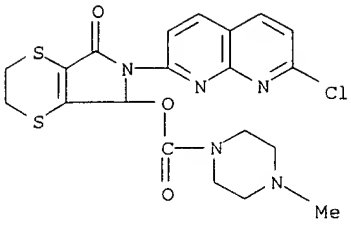
(Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmacol. of, as cyclopyrrolone anxiolytic)
RN 53813-83-5 HCAPLUS
CN 1-Piperazinecarboxylic acid, 4-methyl-, 6-(7-chloro-1,8-naphthyridin-2-yl)-2,3,6,7-tetrahydro-7-oxo-5H-1,4-dithiino[2,3-c]pyrrol-5-yl ester (9CI) (CA INDEX NAME)



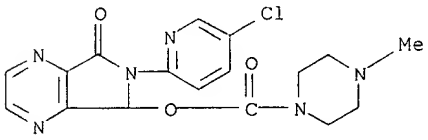
L34 ANSWER 18 OF 55 HCAPLUS COPYRIGHT 2000 ACS
AN 1992:504113 HCAPLUS
DN 117:104113
TI The pharmacology of cyclopyrrolone derivatives acting at the **GABAA** /benzodiazepine **receptor**
AU Doble, A.; Canton, T.; Piot, O.; Zundel, J. L.; Stutzmann, J. M.; Cotrel, C.; Blanchard, J. C.
CS Cent. Rech. Vitry-Alfortville, Rhone-Poulenc Rorer, Vitry-sur-Seine, 94403, Fr.
SO Adv. Biochem. Psychopharmacol. (1992), 47(GABAergic Synaptic Transm.), 407-18
CODEN: ABPYBL; ISSN: 0065-2229
DT Journal
LA English
AB Data accumulated over the last ten years have demonstrated that the cyclopyrrolones, zopiclone and suriclone, are potent allosteric modulators of **GABAA receptor** function, and possess effective hypnotic and anxiolytic advantages compared to benzodiazepines in terms of effects on vigilance and of their propensity for producing **GABAA receptor** sensitivity changes. Binding expts. have revealed that cyclopyrrolones appear to interact with a different binding domain to that of benzodiazepines. This property may underly the pharmacol. differences obsd. in vivo.
IT **43200-80-2**, Zopiclone **53813-83-5**, Suriclone
RL: BIOL (Biological study)
(anxiolytic and hypnotic activity of, **GABAergicA** /benzodiazepine **receptors** in)
RN 43200-80-2 HCAPLUS
CN 1-Piperazinecarboxylic acid, 4-methyl-, 6-(5-chloro-2-pyridinyl)-6,7-dihydro-7-oxo-5H-pyrrolo[3,4-b]pyrazin-5-yl ester (9CI) (CA INDEX NAME)



RN 53813-83-5 HCAPLUS
CN 1-Piperazinecarboxylic acid, 4-methyl-, 6-(7-chloro-1,8-naphthyridin-2-yl)-2,3,6,7-tetrahydro-7-oxo-5H-1,4-dithiino[2,3-c]pyrrol-5-yl ester (9CI) (CA INDEX NAME)

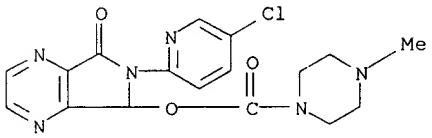


L34 ANSWER 19 OF 55 HCAPLUS COPYRIGHT 2000 ACS
AN 1992:483372 HCAPLUS
DN 117:83372
TI Differential development of tolerance to the depressant effects of benzodiazepine and non-benzodiazepine agonists at the .omega. (BZ) modulatory sites of **GABAA receptors**
AU Sanger, D. J.; Zivkovic, B.
CS Synthelabo Rech., Bagneux, 92220, Fr.
SO Neuropharmacology (1992), 31(7), 693-700
CODEN: NEPHBW; ISSN: 0028-3908
DT Journal
LA English
AB In a previous study, it was found that both the benzodiazepine hypnotic, midazolam, and the imidazopyridine hypnotic, zolpidem, which has selective affinity for a sub-population of .omega. (benzodiazepine, BZ) modulatory sites of **GABAA receptors**, produced similar decreases in rates of food-reinforced lever pressing in rats. However, during 10 days of repeated administration, marked tolerance developed to the depressant effect of midazolam but little tolerance developed with zolpidem. It was found in the present study that, with a within-subject design similar to that used previously, tolerance developed to the response rate-decreasing activity of the benzodiazepine, triazolam and the cyclopyrrolone, zopiclone but not to that of the triazolopyridazine, CL 218,872. In another expt., using a between-groups design, tolerance developed to the effect of midazolam, even if the injections were not assocd. with daily test sessions, providing no evidence for a drug-environment interaction. The lack of tolerance to zolpidem was confirmed in two expts. There was little indication of tolerance to the depressant effect of zolpidem, even after 19 days administration of daily doses, up to 30 mg/kg, a dose 10 times greater than that which completely suppressed responding. These results showed that the extent to which tolerance develops to the effects of drugs with affinity for .omega. (BZ) modulatory sites can show wide variations which may be related to differences in mechanisms of action.
IT **43200-80-2**, Zopiclone
RL: BIOL (Biological study)
(development of tolerance to, as antagonist of omega site of **GABAA receptors**)
RN 43200-80-2 HCAPLUS
CN 1-Piperazinecarboxylic acid, 4-methyl-, 6-(5-chloro-2-pyridinyl)-6,7-dihydro-7-oxo-5H-pyrrolo[3,4-b]pyrazin-5-yl ester (9CI) (CA INDEX NAME)

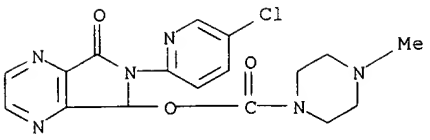


L34 ANSWER 20 OF 55 HCAPLUS COPYRIGHT 2000 ACS
AN 1991:647319 HCAPLUS
DN 115:247319
TI Molecular structure matching by simulated annealing. IV. Classification

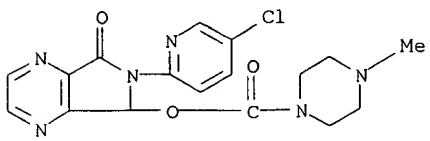
of atom correspondences in sets of dissimilar molecules
AU Papadopoulos, M. C.; Dean, P. M.
CS Dep. Pharmacol., Univ. Cambridge, Cambridge, CB2 1QJ, UK
SO J. Comput.-Aided Mol. Des. (1991), 5(2), 119-33
CODEN: JCADEQ; ISSN: 0920-654X
DT Journal
LA English
AB A set of 6 mols., active at the benzodiazepine **GABAA receptor** site, are matched pairwise with one member of the set in turn. Matchings are performed by simulated annealing using null correspondences to reject poorly matched atom positions. Cluster anal. is employed to identify mol. similarities after an optimal mol. superimposition has been discovered. A statistic for the compactness of clustered atom positions is suggested. The introduction of null correspondence causes the clusters of matched atoms to become more compact.
IT **43200-80-2**, Zopiclone
RL: BIOL (Biological study)
(mol. pairing of, for simulated annealing, in mol. structure matching)
RN 43200-80-2 HCAPLUS
CN 1-Piperazinecarboxylic acid, 4-methyl-, 6-(5-chloro-2-pyridinyl)-6,7-dihydro-7-oxo-5H-pyrrolo[3,4-b]pyrazin-5-yl ester (9CI) (CA INDEX NAME)



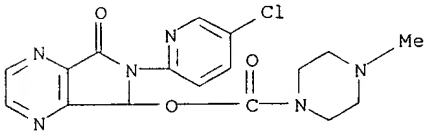
L34 ANSWER 21 OF 55 HCAPLUS COPYRIGHT 2000 ACS
AN 1991:55662 HCAPLUS
DN 114:55662
TI Differences in pharmacological profiles of a new generation of benzodiazepine and non-benzodiazepine hypnotics
AU Perrault, Ghislaine; Morel, Eliane; Sanger, David J.; Zivkovic, Branimir
CS Synthelabo Rech., Bagneux, 92220, Fr.
SO Eur. J. Pharmacol. (1990), 187(3), 487-94
CODEN: EJPHAZ; ISSN: 0014-2999
DT Journal
LA English
AB The hypnotics, quazepam (a benzodiazepine), brotizolam (a thienotriazolodiazepine), zopiclone (a cyclopyrrolone) and zolpidem (an imidazopyridine) have a common ability to bind to the benzodiazepine recognition site (.omega. **receptor**) within the **GABAA receptor**. For this reason, their pharmacol. profiles were compared in mice. All compds. shared anticonvulsant and central depressant effects. However, the sedative activity of zolpidem appeared at much lower doses than did the anticonvulsant and myorelaxant effects but the opposite was obsd. with the other hypnotics. In contrast to brotizolam, quazepam and zopiclone, zolpidem did not increase food intake in mice placed in a novel environment, indicating that this drug lacks disinhibitory activity. Moreover, the efficacy of zolpidem at the **GABAA receptor**, as indicated by its activity against convulsions induced by the GABA synthesis inhibitor, isoniazid, was much greater than that of other hypnotics. These results suggest that the hypnoselective properties obsd. with zolpidem might be related to a high selectivity for the .omega.1 recognition site of the **GABAA receptor** coupled with a very high intrinsic activity.
IT **43200-80-2**, Zopiclone
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmacol. of, benzodiazepine .omega.1 receptor interaction in relation to)
RN 43200-80-2 HCAPLUS
CN 1-Piperazinecarboxylic acid, 4-methyl-, 6-(5-chloro-2-pyridinyl)-6,7-dihydro-7-oxo-5H-pyrrolo[3,4-b]pyrazin-5-yl ester (9CI) (CA INDEX NAME)



L34 ANSWER 22 OF 55 HCAPLUS COPYRIGHT 2000 ACS
AN 1991:35893 HCAPLUS
DN 114:35893
TI The activity of zolpidem and other hypnotics within the .**gamma**.-**aminobutyric acid** (**GABAA**) **receptor** supramolecular complex, as determined by 35S-t-butylbicyclophosphorothionate (35S-TBPS) binding to rat cerebral cortex membranes
AU Lloyd, G. K.; Danielou, G.; Thuret, F.
CS Synthelabo Rech., Bagneux, Fr.
SO J. Pharmacol. Exp. Ther. (1990), 255(2), 690-6
CODEN: JPETAB; ISSN: 0022-3565
DT Journal
LA English
AB The present study compares the effects of different hypnotics acting at .omega.1/.omega.2 sites (zolpidem, zopiclone, flunitrazepam, and triazolam) on 35S-t-butylbicyclophosphorothionate (35S-TBPS) binding to well-washed rat cerebral membranes, in the presence of 1M NaCl. Under these conditions, all compds. enhanced 35S-TBPS binding in the 0.05 to 10.mu.M range with EC50 values and maximal enhancement of: zolpidem, 84 nM and 35%; flunitrazepam, 8 nM and 41%; zopiclone, 171 nM and 51%; triazolam, 2 nM and 42%. Under these conditions, .gamma.-aminobutyric acid enhanced 35S-TBPS binding with an EC50 of 240 nM and a 38% maximal increase. The EC50 values for the stimulation of 35S-TBPS binding are well correlated, with (r = 0.97) the affinity of these compds. at .omega.1/.omega.2 sites, and are in the same concn. range. This enhanced binding was due to an altered apparent affinity for the 35S-TBPS recognition site without any change in the no. of sites (Scatchard anal.). The effect of zolpidem and other hypnotics was antagonized by flumazenil. This was an apparently competitive antagonism in the case of zolpidem or flunitrazepam, whereas for zopiclone, increased the concn. of the hypnotic did not overcome the antagonism. Bicuculline only partially antagonized the hypnotic-induced enhancement of 35S-TBPS binding. This antagonism was more effective for zopiclone (-57%) than for either zolpidem (-33%) or flunitrazepam (-30%). Zolpidem and the other hypnotics studied induced a fast component of dissocn. which was not obsd. in the control membranes. These findings are consistent with the hypothesis that .omega.1/.omega.2 agonists increase the frequency of openings of the chloride ionophore, with both .**gamma**.-**aminobutyric acid**-A **receptor**-dependent and -independent mechanisms.
IT **43200-80-2**, Zopiclone
RL: BIOL (Biological study)
(**GABAA receptor** complex response to zolpidem and, of brain, TBPS binding in detn. of)
RN 43200-80-2 HCAPLUS
CN 1-Piperazinecarboxylic acid, 4-methyl-, 6-(5-chloro-2-pyridinyl)-6,7-dihydro-7-oxo-5H-pyrrolo[3,4-b]pyrazin-5-yl ester (9CI) (CA INDEX NAME)



L34 ANSWER 23 OF 55 HCAPLUS COPYRIGHT 2000 ACS
AN 1991:17503 HCAPLUS
DN 114:17503
TI Preferential decrease in dopamine utilization in prefrontal cortex by zopiclone, diazepam and zolpidem in unstressed rats
AU Boireau, A.; Dubedat, P.; Laduron, P. M.; Doble, A.; Blanchard, J. C.
CS Cent. Rech. Vitry-Alfortville, Rhone-Poulenc Sante, Vitry-sur-Seine, 94403, Fr.
SO J. Pharm. Pharmacol. (1990), 42(8), 562-5
CODEN: JPPMAB; ISSN: 0022-3573
DT Journal
LA English
AB This study has compared the effects of a cyclopyrrolone, zopiclone, a benzodiazepine, diazepam, and an imidazopyridine, zolpidem, on dopamine (DA) and DOPAC levels, and DA utilization (DOPAC/DA ratio) in rat striatum and prefrontal cortex. The endogenous levels of DA were significantly increased by both zopiclone (2.5, 10 and 40 mg/kg oral) and diazepam (10 and 40 mg/kg oral) in the prefrontal cortex, whereas striatal DA content was significantly increased only with the highest dose of diazepam (40 mg/kg oral). Diazepam (10 and 40 mg/kg oral) decreased cortical level of DOPAC more markedly than striatal levels, whereas zopiclone (40 mg/kg oral) only slightly decreased striatal DOPAC levels. Zopiclone and diazepam dose-dependently decreased DA utilization, an effect which was more markedly in prefrontal cortex than in striatum. This result was confirmed with zolpidem, another benzodiazepine ligand. Zopiclone was most potent at decreasing DA utilization at the cortical level. The diazepam-induced decreases in DA metab. and utilization were antagonized by Ro 15-1788, suggesting that the effects seen were mediated by specific benzodiazepine receptors. Thus, the results clearly show that ligands acting on the benzodiazepine **receptor/GABA receptor**/chloride ionophore complex can decrease the utilization of dopamine in unstressed rats. The preferential decrease in cortical DA utilization induced by benzodiazepine ligands may be compared to the well-known activation by stress of the mesocortical DAergic system.
IT **43200-80-2**, Zopiclone
RL: BIOL (Biological study)
(dopamine utilization in prefrontal cortex inhibition by, benzodiazepine receptor binding and anxiolytic activity in relation to)
RN 43200-80-2 HCAPLUS
CN 1-Piperazinecarboxylic acid, 4-methyl-, 6-(5-chloro-2-pyridinyl)-6,7-dihydro-7-oxo-5H-pyrrolo[3,4-b]pyrazin-5-yl ester (9CI) (CA INDEX NAME)

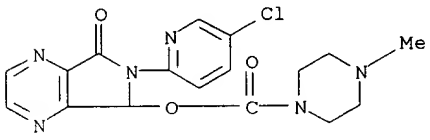


L34 ANSWER 24 OF 55 HCAPLUS COPYRIGHT 2000 ACS
AN 1991:499 HCAPLUS
DN 114:499
TI Cyclopyrrolones, unlike some benzodiazepines, do not induce physical dependence in mice
AU Piot, O.; Betschart, J.; Stutzmann, J. M.; Blanchard, J. C.
CS Cent. Rech. Vitry-Alfortville, Rhone-Poulenc Sante, Vitry sur Seine, F-94403, Fr.
SO Neurosci. Lett. (1990), 117(1-2), 140-3
CODEN: NELED5; ISSN: 0304-3940
DT Journal
LA English
AB In a model of phys. dependence in mice, treatment with cyclopyrrolones such as zopiclone and suriclone (from 4 to 400 mg/kg/day), did not modify the sensitivity of the **.gamma.-aminobutyric acid (GABA) receptor** complex to the partial inversion agonist FG 7142 following their withdrawal, whereas sensitivity changes were obsd. after treatment and withdrawal from some

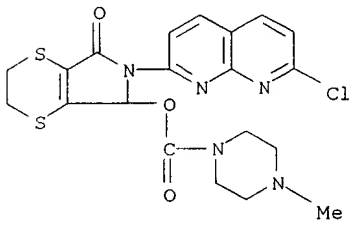
benzodiazepines (e.g. lorazepam, diazepam, flunitrazepam and triazolam). These data suggest that, in contrast to some benzodiazepines, zopiclone and suriclone may not produce phys. dependence.

IT **43200-80-2**, Zopiclone **53813-83-5**, Suriclone
RL: PRP (Properties)
(phys. dependence potential of)

RN 43200-80-2 HCAPLUS
CN 1-Piperazinecarboxylic acid, 4-methyl-, 6-(5-chloro-2-pyridinyl)-6,7-dihydro-7-oxo-5H-pyrrolo[3,4-b]pyrazin-5-yl ester (9CI) (CA INDEX NAME)



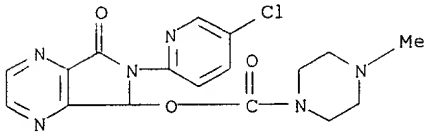
RN 53813-83-5 HCAPLUS
CN 1-Piperazinecarboxylic acid, 4-methyl-, 6-(7-chloro-1,8-naphthyridin-2-yl)-2,3,6,7-tetrahydro-7-oxo-5H-1,4-dithiino[2,3-c]pyrrol-5-yl ester (9CI) (CA INDEX NAME)



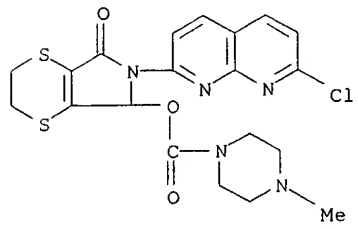
L34 ANSWER 25 OF 55 HCAPLUS COPYRIGHT 2000 ACS
AN 1990:565947 HCAPLUS
DN 113:165947
TI Effects of GABA and anxiolytics on the single unit discharge of suprachiasmatic neurons in rat hypothalamic slices
AU Liou, S. Y.; Shibata, S.; Albers, H. E.; Ueki, S.
CS Lab. Neuroendocrinol. Behav., Georgia State Univ., Atlanta, GA, 30303, USA
SO Brain Res. Bull. (1990), 25(1), 103-7
CODEN: BRBUDU; ISSN: 0361-9230
DT Journal
LA English
AB The effects of GABA, muscimol, baclofen, and the anxiolytics diazepam (DZP), flurazepam (FZP), and zopiclone on single-unit neural activities in the suprachiasmatic nucleus (SCN) were investigated using the rat hypothalamic slice prepn. Exposure of the slice to GABA (10-4M) produced inhibitory responses in 65% of the 49 SCN neurons examd. The threshold concn. of GABA ranged 10-6-10-4M. Neurons responsive to GABA were not restricted to a subdivision of the SCN, but were diffusely distributed throughout the nucleus. DZP, FZP, and zopiclone produced responses similar to those of GABA. The inhibitory effects of GABA (10-5 M) were potentiated by coadministration of DZP (10-5 M). Muscimol and baclofen (10-7-10-4M) also inhibited SCN neuronal activity in a dose-dependent manner. Bicuculline (10-5-10-4 M) scarcely affected the baclofen-induced inhibition (1/6) but strongly antagonized the effects of muscimol, GABA, and DZP. These results suggest that the **receptors** mediating the inhibitory effects of **GABA** and anxiolytics within the SCN may be GABAA and(or) **GABAB** or **GABA**-BDZ **receptor** complex, resp.

IT **43200-80-2**, Zopiclone
RL: BIOL (Biological study)
(suprachiasmatic nucleus unit activity response to, GABA in relation to)

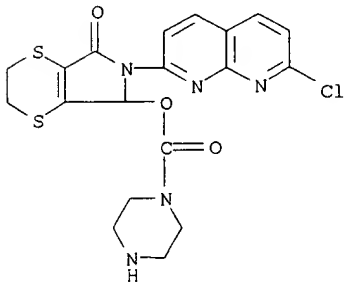
RN 43200-80-2 HCAPLUS
CN 1-Piperazinecarboxylic acid, 4-methyl-, 6-(5-chloro-2-pyridinyl)-6,7-dihydro-7-oxo-5H-pyrrolo[3,4-b]pyrazin-5-yl ester (9CI) (CA INDEX NAME)



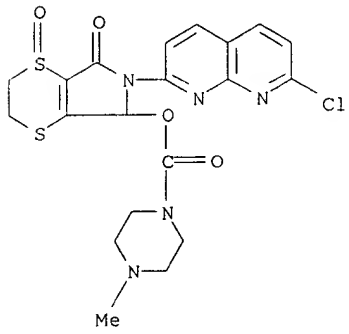
L34 ANSWER 26 OF 55 HCAPLUS COPYRIGHT 2000 ACS
AN 1990:111927 HCAPLUS
DN 112:111927
TI Interaction of suriclone with central type benzodiazepine receptors in living baboons
AU Brouillet, Emmanuel; Chavoix, Chantal; Hantraye, Philippe; Kunimoto, Masayuki; Khalili-Varasteh, Marina; Chevalier, Paul; Frydman, Armand; Gaillot, Jean; Prenant, Christian; et al.
CS Serv. Hosp. Frederic Joliot, Orsay, 91406, Fr.
SO Eur. J. Pharmacol. (1990), 175(1), 49-55
CODEN: EJPHAZ; ISSN: 0014-2999
DT Journal
LA English
AB The interaction of suriclone and two of its main metabolites with central type benzodiazepine receptors, which had been labeled in vivo with the radioligand [14C]RO 15-1788, was investigated in baboons. The concn. of radioligand bound to the receptors, as measured in brain transverse sections by positron emission tomog., decreased rapidly after the i.v. administration of suriclone at doses known to induce pharmacol. effects. Te rate and extent to which [11C]RO 15-1788 binding was displaced increased with increasing doses of suriclone. The half-ID was 0.08 mg/kg. The rapid inhibitory effect of suriclone on the in vivo binding of [14C]RO 15-1788 in the brain seems to reflect its ability to act at the **GABA**-benzodiazepine **receptor** complex, at or near the benzodiazepine binding site, to induce its pharmacol. activity. The i.v. injection of the demethylated metabolite of suriclone, RP 35,489, caused only a slight displacement of [14C]RO 15-1788 binding even at 2 mg/kg. Thus, suriclone appears to be more potent than RP 35,489 is displacing the benzodiazepine antagonist in vivo. The sulfoxide metabolite, RP 46,166, did not change the kinetics of [11C]RO 15-1788 binding in the brain. The slight effects produced by high doses of RP 35,489 and RP 46,166 on [14C]Ro 15-1788 binding in the brain suggest that these metabolites are probably not responsible for the biol. activity of suriclone mediated by benzodiazepine receptors.
IT **53813-83-5**, Suriclone **59878-27-2**, RP 35489
94342-73-1
RL: PROC (Process)
(binding of, to benzodiazepine receptors of brain)
RN 53813-83-5 HCAPLUS
CN 1-Piperazinecarboxylic acid, 4-methyl-, 6-(7-chloro-1,8-naphthyridin-2-yl)-2,3,6,7-tetrahydro-7-oxo-5H-1,4-dithiino[2,3-c]pyrrol-5-yl ester (9CI) (CA INDEX NAME)



RN 59878-27-2 HCAPLUS
CN 1-Piperazinecarboxylic acid, 6-(7-chloro-1,8-naphthyridin-2-yl)-2,3,6,7-tetrahydro-7-oxo-5H-1,4-dithiino[2,3-c]pyrrol-5-yl ester (9CI) (CA INDEX NAME)

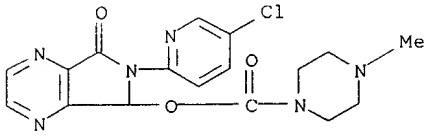


RN 94342-73-1 HCAPLUS
CN 1-Piperazinecarboxylic acid, 4-methyl-, 6-(7-chloro-1,8-naphthyridin-2-yl)-2,3,6,7-tetrahydro-1-oxido-7-oxo-5H-1,4-dithiino[2,3-c]pyrrol-5-yl ester (9CI) (CA INDEX NAME)

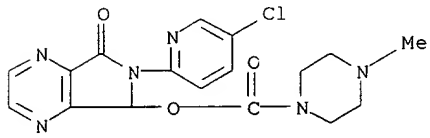


L34 ANSWER 27 OF 55 HCAPLUS COPYRIGHT 2000 ACS
AN 1990:69778 HCAPLUS
DN 112:69778
TI Inhibition constants and GABA-shifts at 2.degree.C and 37.degree.C for a spectrum of ligands acting on the benzodiazepine receptors of guinea pig hippocampus
AU Dawson, Raymond M.; Poretski, Michael
CS Mater. Res. Lab., Def. Sci. Technol. Organ., Ascot Vale, 3032, Australia
SO Gen. Pharmacol. (1989), 20(6), 843-8
CODEN: GEPHDP; ISSN: 0306-3623
DT Journal
LA English
AB Dissocn. consts. and Hill coeffs. were detd. for 13 ligands inhibiting the binding of [3H]flunitrazepam to the benzodiazepine receptor of guinea pig hippocampus at 2.degree. and 37.degree.. The ratio of I50 in the absence of GABA to that in the presence of 10-5M GABA (the GABA-shift) varied 0.4-2.5. There was no correlation between the pharmacol. activity of the ligand and the GABA-shift, or between the pharmacol. activity and the magnitude of the increase in affinity of the ligand for the receptor as the temp. decreased from 37.degree. to 2.degree.. A correlation was obsd. between the temp.-induced affinity change and the GABA-shift at 37.degree..
IT **43200-80-2**, Zopiclone
RL: BIOL (Biological study)
(benzodiazepine **receptor** binding of, in hippocampus, **GABA** effect on, temp. in relation to)

RN 43200-80-2 HCAPLUS
CN 1-Piperazinecarboxylic acid, 4-methyl-, 6-(5-chloro-2-pyridinyl)-6,7-dihydro-7-oxo-5H-pyrrolo[3,4-b]pyrazin-5-yl ester (9CI) (CA INDEX NAME)



L34 ANSWER 28 OF 55 HCAPLUS COPYRIGHT 2000 ACS
AN 1989:417562 HCAPLUS
DN 111:17562
TI Effects of benzodiazepine and GABA antagonists on anticonflict effects of antianxiety drugs injected into the rat amygdala in a water-lick suppression test
AU Shibata, Shigenobu; Yamashita, Kimihiro; Yamamoto, Etsuko; Ozaki, Tohru; Ueki, Showa
CS Fac. Pharm. Sci., Kyushu Univ., Fukuoka, 812, Japan
SO Psychopharmacology (Berlin) (1989), 98(1), 38-44
CODEN: PSCHDL; ISSN: 0033-3158
DT Journal
LA English
AB In order to elucidate the role of the amygdala in rat conflict behavior in a water lick suppression test, the effect of lesions of various nuclei of the amygdaloid complex on this behavior was examd. An anticonflict effect was produced by a lesion of the anterior part of central and basolateral amygdala, and a lesion to the posterior part of the central amygdala, but not by lesions to the posterior of the basolateral amygdala or the medial amygdala. In a second expt., the effects of benzodiazepine- and GABA-antagonists on the anticonflict action of diazepam, zopiclone, and phenobarbital injected into the anterior part of central and basolateral amygdala were examd., also using a water lick suppression test. The order of potency for anticonflict action was lormetazepam > zopiclone .gtoreq. diazepam > flurazepam .gtoreq. phenobarbital for both systemic administration or by intra-amygdala injection. The anticonflict effects of diazepam and zopiclone injected into the amygdala were completely reversed by Ro15-1788 and .beta.-CCM but not by bicuculline, while the anticonflict effect on phenobarbital was reversed by .beta.-CCM but not by Ro15-1788 or bicuculline. The present results strongly suggest that the anterior nuclei of central and basolateral amygdala are important sites of action of antianxiety drugs, and that an anticonflict action produced by intra-amygdala injection of benzodiazepines or barbiturate is mediated through the different receptor mechanisms.
IT **43200-80-2**, Zopiclone
RL: BIOL (Biological study)
(conflict behavior inhibition by, brain amygdala mediation of, receptors in)
RN 43200-80-2 HCAPLUS
CN 1-Piperazinecarboxylic acid, 4-methyl-, 6-(5-chloro-2-pyridinyl)-6,7-dihydro-7-oxo-5H-pyrrolo[3,4-b]pyrazin-5-yl ester (9CI) (CA INDEX NAME)



L34 ANSWER 29 OF 55 HCAPLUS COPYRIGHT 2000 ACS
AN 1988:604822 HCAPLUS
DN 109:204822
TI In vivo determination of the profile of benzodiazepine ligands by

comparing the inhibition of 3H-Ro 15-1788 binding to the modulation of cGMP levels in mouse cerebellum

AU Boireau, A.; Martel, M.; Farges, G.; Dubedat, P.; Laduron, P. M.; Blanchard, J. C.

CS Cent. Rech. Vitry, Rhone-Poulenc Sante, Vitry-sur-Seine, 94403, Fr.

SO Biochem. Pharmacol. (1988), 37(19), 3765-9
CODEN: BCPCA6; ISSN: 0006-2952

DT Journal

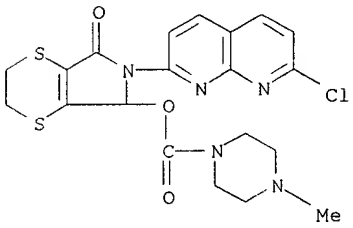
LA English

AB The in vivo effects of various benzodiazepine (BZD) ligands belonging to different chem. families were studied comparatively in mouse cerebellum by using displacement of [3H]Ro 15-1788 binding and cGMP content as biochem. tools. It was possible to differentiate 4 classes of compds. with regard to these biochem. parameters. The 1st class of compds. such as diazepam and suriclone induced a net effect on in vivo [3H]Ro 15-1788 binding and a dose-dependent decrease of cGMP levels. A 2nd class of drugs such as ZK 91296 and CGS 9896 showed in vivo activities in displacement studies but relatively small or moderate activities on cGMP levels. A 3rd class was represented by Ro 15-1788 itself which prevented dose-dependently the in vivo [3H]Ro 15-1788 binding but was devoid of effect on cGMP levels. Finally, a 4th class of compds. (CGS 8216, FG 7142, .beta.-CCM, and DMCM) showed in vivo displacement of [3H]Ro 15-1788 with a concomitant increase of cGMP levels. The 1st class of compds. represents full agonists, the 2nd class, partial agonists, the 3rd class, the antagonist Ro-15-1788 itself, and the 4th class corresponds to inverse agonists. Thus, [3H]Ro 15-1788 binding and cGMP levels can be used to differentiate in vivo BZD ligands acting on the BZD **receptor/GABA receptor**/chloride ionophore complex.

IT **53813-83-5**, Suriclone
RL: BIOL (Biological study)
(as benzodiazepine receptor agonist, Ro 15-1788 displacement and cerebellar cGMP response in relation to)

RN 53813-83-5 HCAPLUS

CN 1-Piperazinecarboxylic acid, 4-methyl-, 6-(7-chloro-1,8-naphthyridin-2-yl)-2,3,6,7-tetrahydro-7-oxo-5H-1,4-dithiino[2,3-c]pyrrol-5-yl ester (9CI) (CA INDEX NAME)



L34 ANSWER 30 OF 55 HCAPLUS COPYRIGHT 2000 ACS

AN 1988:584035 HCAPLUS

DN 109:184035

TI Differentiation of activities within the GABAA-chloride ionophore complex by means of 35S-TBPS binding

AU Lloyd, K. G.; Danielou, G.; Thuret, F.

CS Lab. Etud., Rech. Synthelabo, Bagneux, 92220, Fr.

SO Adv. Biochem. Psychopharmacol. (1988), 45(Chloride Channels Their Modulation Neurotransm. Drugs), 199-207
CODEN: ABPYBL; ISSN: 0065-2229

DT Journal

LA English

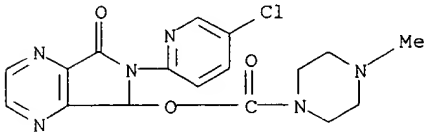
AB [35S]-tert-butylbicyclophosphorothionate ([35S]TBPS) was used to label the Cl- ionophore of the GABAergic-Cl- ionophore complex to investigate the interaction between .omega.1 and .omega.2 recognition sites of this complex with the Cl- ionophore. The anxiolytics (alpiden and clonazepam) and the hypnotics (zolpidem, flunitrazepam, and zopiclone) enhance TBPs binding within a dose range correlating with their therapeutic plasma levels and their affinity for .omega.1/.omega.2 receptors. However, a

different degree of linkage for different compds. apparently occurs between the **GABAergicA receptor-** and the .omega.1/.omega.2 receptor-mediated enhancement of TBPS binding, as the action of alpidem is completely reversed by bicuculline, whereas for zolpidem and flunitrazepam a component of the TBPS enhancement is bicuculline insensitive. A Ro 5-4864-sensitive site [probably not the .omega.3 site) also occurs with the **GABAergicA receptor** supramol. complex, which also participates in the enhancement of TBPS binding. Thus, there are different recognition sites within the **GABAergic receptor** supramol. complex, all of which have characteristic effects on the Cl- ionophore.

IT **43200-80-2**, Zopiclone
RL: BIOL (Biological study)
(chloride ionophore of **GABAergicA receptor** interaction with)

RN 43200-80-2 HCAPLUS

CN 1-Piperazinecarboxylic acid, 4-methyl-, 6-(5-chloro-2-pyridinyl)-6,7-dihydro-7-oxo-5H-pyrrolo[3,4-b]pyrazin-5-yl ester (9CI) (CA INDEX NAME)



L34 ANSWER 31 OF 55 HCAPLUS COPYRIGHT 2000 ACS

AN 1988:542489 HCAPLUS

DN 109:142489

TI Effects of nonsedative anxiolytic drugs on responses to GABA and on diazepam-induced enhancement of these responses on mouse neurons in cell culture

AU De Deyn, Peter P.; Macdonald, Robert L.

CS Neurosci. Lab. Building, Univ. Michigan, Ann Arbor, MI, 48104, USA

SO Br. J. Pharmacol. (1988), 95(1), 109-20
CODEN: BJPCBM; ISSN: 0007-1188

DT Journal

LA English

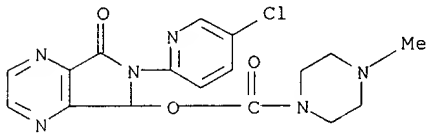
AB Intracellular microelectrode recording techniques were performed on mouse spinal cord and cerebral hemisphere neurons grown in primary dissocd. cell culture. The effects of several anxiolytics applied by local pressure ejection on responses to GABA evoked by iontophoresis were investigated. Responses to GABA were depolarizing, since intracellular Cl- concn. was increased by injection from KCl (3 M)-filled recording micropipettes and neurons were held at large neg. membrane potentials (-70 to 90 mV). The agents studied were 6 "nonsedative anxiolytics", CL 218,872, PK 8165, PK 9084, CGS 9896, ZK 91296, and buspirone, and 2 sedative anxiolytics, diazepam and zopiclone. Direct effects on response to GABA were studied for all drugs applied in varying concns. For the drugs which altered responses to **GABA**, the effects of the benzodiazepine **receptor** antagonists Ro 15-1788 and CGS 8216 were evaluated. For the drugs devoid of significant effect on responses to GABA, the influence on diazepam-induced enhancement of responses to GABA was evaluated. Diazepam, zopiclone and CL 218,872 concn.-dependently and reversibly enhanced responses to GABA. Maximal enhancement was 82% for diazepam (500 nM), 64% for zopiclone (10 .mu.M) and 20% for CL 218,72 (10 .mu.M). PK 8165 effects varied with concn., enhancing responses to GABA (up to 18%) at nanomolar concns. and reducing responses to GABA (up to 90%) at micromolar concns. CGS 9896, ZK 91296, PK 9084 and buspirone, in concns. ranging from 1 nM to 10 .mu.M, lacked significant direct effects on responses to GABA. The enhancing effects of diazepam, zopiclone, CL 218,872 and PK 8165 were antagonized by Ro 15-1788. However, the inhibitory effect on responses to GABA of PK 8165 at micromolar concns. was not antagonized by CGS 8216. CGS 9896 and ZK 91296 concn.-dependently blocked the diazepam-induced enhancement of responses to GABA. However, PK 9084 and buspirone did not antagonize the diazepam-induced enhancement of responses to GABA. These results indicate that diazepam and zopiclone

may be full agonists, CL 218,872 and PK 8165 are partial agonists, and CGS 9896 and ZK 91296 are pure antagonists at benzodiazepine receptors. On the other hand, PK 9084 and buspirone do not interact with benzodiazepine receptors.

IT **43200-80-2**, Zopiclone
RL: BIOL (Biological study)
(benzodiazepine **receptors** and **GABA** effects in neurons of brain and spinal cord response to)

RN 43200-80-2 HCAPLUS

CN 1-Piperazinecarboxylic acid, 4-methyl-, 6-(5-chloro-2-pyridinyl)-6,7-dihydro-7-oxo-5H-pyrrolo[3,4-b]pyrazin-5-yl ester (9CI) (CA INDEX NAME)



L34 ANSWER 32 OF 55 HCAPLUS COPYRIGHT 2000 ACS

AN 1988:431376 HCAPLUS

DN 109:31376

TI Zopiclone, a cyclopyrrolone hypnotic: review of properties

AU Brun, J. P.

CS Rhone Poulenc Sante, Antony, 92165, Fr.

SO Pharmacol., Biochem. Behav. (1988), 29(4), 831-2
CODEN: PBBHAU; ISSN: 0091-3057

DT Journal; General Review

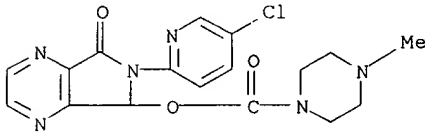
LA English

AB A review with 4 refs. examg. the preclin. and clin. profiles of the nonbenzodiazepine hypnotic zopiclone, which binds to the **GABA** complex at a nonbenzodiazepine **receptor** site.

IT **43200-80-2**, Zopiclone
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmacol. of, in humans and lab. animals)

RN 43200-80-2 HCAPLUS

CN 1-Piperazinecarboxylic acid, 4-methyl-, 6-(5-chloro-2-pyridinyl)-6,7-dihydro-7-oxo-5H-pyrrolo[3,4-b]pyrazin-5-yl ester (9CI) (CA INDEX NAME)



L34 ANSWER 33 OF 55 HCAPLUS COPYRIGHT 2000 ACS

AN 1988:143313 HCAPLUS

DN 108:143313

TI The effect of agonists at the **GABA**-benzodiazepine-**receptor**-complex on the proconflict effect induced by .beta.-CCM and pentetrazole in rats

AU Nagatani, Tadashi; Yamamoto, Tsuneyuki; Sugihara, Taisuke; Ueki, Showa

CS Fac. Pharm. Sci., Kyushu Univ., Fukuoka, 812, Japan

SO Jpn. J. Pharmacol. (1988), 46(3), 267-74
CODEN: JJPAAZ; ISSN: 0021-5198

DT Journal

LA English

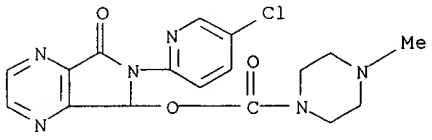
AB The effect of methyl-.beta.-carboline-3-carboxylate (.beta.-CCM) and anxiolytics (diazepam, zopiclone, and phenobarbital) on the proconflict effects of .beta.-CCM and pentetrazole (PTZ) was studied in rats. .beta.-CCM and PTZ appeared to exert their proconflict effects through the depression of the GABAergic function by interacting with the

GABA/benzodiazepine/barbiturate and a Cl- ionophore complex. Anxiolytics reduced the proconflict effect induced by these 2 agents through a facilitation of GABAergic function. Propyl-.beta.-carboline-3-carboxylate seems to be an antagonist like Ro 15-1788. The mechanism for the prolonged latency induced by .beta.-CCM and PTZ is different from that of the proconflict effect.

IT **43200-80-2**, Zopiclone
RL: BIOL (Biological study)
(methylcarbolinecarboxylate and pentetrazole-induced proconflict response to, anxiolytic mechanism in relation to)

RN 43200-80-2 HCAPLUS

CN 1-Piperazinecarboxylic acid, 4-methyl-, 6-(5-chloro-2-pyridinyl)-6,7-dihydro-7-oxo-5H-pyrrolo[3,4-b]pyrazin-5-yl ester (9CI) (CA INDEX NAME)



L34 ANSWER 34 OF 55 HCAPLUS COPYRIGHT 2000 ACS

AN 1987:629063 HCAPLUS

DN 107:229063

TI The effect of agonists at the **GABA**-benzodiazepine **receptor** complex on the duration of immobility of mice in the forced swimming test

AU Nagatani, Tadashi; Yamamoto, Tsuneyuki; Sugihara, Taisuke; Ueki, Showa

CS Fac. Pharm. Sci., Kyushu Univ., Fukuoka, 812, Japan

SO Eur. J. Pharmacol. (1987), 142(1), 17-22
CODEN: EJPHAZ; ISSN: 0014-2999

DT Journal

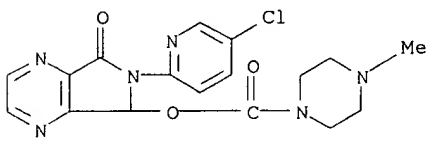
LA English

AB The effect of various agents which affect in a different manner the **GABA**-benzodiazepine **receptor**-Cl- ionophore complex was studied in relation to the immobile behavior of mice in the forced-swimming test. Diazepam, flurazepam, pentobarbital, phenobartital, zopiclone, and .beta.-CCP (propyl-.beta.-carboline-3-carboxylate) enhanced immobility in a dose-dependent manner. In the doses used, these agents had almost no muscle-relaxant action. Ro 15-1788 and .beta.-CCM (methyl-.beta.-carboline-3-carboxylate) had no effect on the duration of immobility. However, Ro 15-1788 and .beta.-CCM reversed the enhancing effect produced by the other 6 drugs. The enhancement of the duration of immobility of mice may correlate with the anxiolytic action, but not the muscle-relaxant action. The effect may be mainly mediated by the benzodiazepine receptor, which forms a part of the **GABA** -benzodiazepine **receptor**-Cl- ionophore complex. There may be similarities in the behavioral effects of .beta.-CCP and benzodiazepines.

IT **43200-80-2**, Zopiclone
RL: BIOL (Biological study)
(immobile behavior response to, benzodiazepine receptors in relation to)

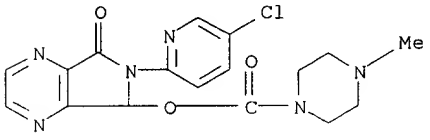
RN 43200-80-2 HCAPLUS

CN 1-Piperazinecarboxylic acid, 4-methyl-, 6-(5-chloro-2-pyridinyl)-6,7-dihydro-7-oxo-5H-pyrrolo[3,4-b]pyrazin-5-yl ester (9CI) (CA INDEX NAME)



L34 ANSWER 35 OF 55 HCAPLUS COPYRIGHT 2000 ACS

AN 1987:470676 HCAPLUS
DN 107:70676
TI Modification of GABA turnover in the striatum and hippocampus of the rat after zopiclone
AU Zambotti, F.; Zonta, N.; Hafner, B.; Ferrario, P.; Zecca, L.; Mantegazza, P.
CS Sch. Med., Univ. Milan, Milan, I-20129, Italy
SO Naunyn-Schmiedeberg's Arch. Pharmacol. (1987), 335(5), 547-50
CODEN: NSAPCC; ISSN: 0028-1298
DT Journal
LA English
AB The effects of zopiclone, a non-benzodiazepine compd. that interacts with benzodiazepine **receptors**, on **GABA** turnover rate and **GABA** content in the rat striatum and hippocampus have been studied. I.p. administration of zopiclone reduced the GABA turnover rates in both the striatum and hippocampus, as estd. from the rate of GABA accumulation after inhibition of GABA transaminase by aminooxyacetic acid (AOAA). The effect of zopiclone on AOAA-induced accumulation of GABA in the hippocampus and striatum was blocked by the i.p. injection of the benzodiazepine receptor antagonist Ro 15-3505. Furthermore, zopiclone slightly but significantly decreased GABA content in the hippocampus, the decrease being blocked by coadministration of the benzodiazepine receptor antagonist Ro 15-1788. These results confirm that the GABAergic system plays a role in the mechanism of action of zopiclone.
IT **43200-80-2**, Zopiclone
RL: BIOL (Biological study)
(GABA-turnover in striatum and hippocampus response to)
RN 43200-80-2 HCAPLUS
CN 1-Piperazinecarboxylic acid, 4-methyl-, 6-(5-chloro-2-pyridinyl)-6,7-dihydro-7-oxo-5H-pyrrolo[3,4-b]pyrazin-5-yl ester (9CI) (CA INDEX NAME)



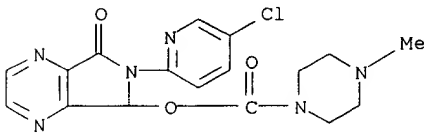
L34 ANSWER 36 OF 55 HCAPLUS COPYRIGHT 2000 ACS
AN 1987:432608 HCAPLUS
DN 107:32608
TI Stereochemical features controlling binding and intrinsic activity properties of benzodiazepine-receptor ligands
AU Borea, Pier Andrea; Gilli, Gastone; Bertolasi, Valerio; Ferretti, Valeria
CS Ist. Farmacol., Univ. Ferrara, Ferrara, 44100, Italy
SO Mol. Pharmacol. (1987), 31(4), 334-44
CODEN: MOPMA3; ISSN: 0026-895X
DT Journal
LA English
AB Benzodiazepine-receptor ligands belong to several different chem. classes. All of them bind to the receptor but display a variety of biol. effects ranging from agonist to inverse agonist to antagonist. The properties of the most representative compds. for each class are briefly reviewed as concerns their **receptor** binding affinities, .**gamma**.-**aminobutyric acid** ratios, photoaffinity labeling ratios, and pharmacol. properties. Their geometries, as obtained by X-ray crystallog., are discussed and missing crystal and mol. structures of 2 of them (zopiclone and CL 218-872) are reported. Binding and intrinsic activity properties of series of benzodiazepines and .beta.-carbolines are extensively analyzed and correlated with their mol. structures. A general stereochem. model accounting for both binding abilities and kinds of biochem. and pharmacol. activities for all benzodiazepine-receptor ligands is proposed. This is based on the assumption of a rather diffuse and substantially planar recognition site where the main drug-receptor interactions are mediated by the drug carbonylic or iminic groups via hydrogen bonding and the obsd. differences in pharmacol. profiles are accounted for by the different localization of the different ligands

inside this unique binding site.

IT **43200-80-2**, Zopiclone
RL: BIOL (Biological study)
(mol. and crystal structure of, benzodiazepine receptor binding in relation to)

RN 43200-80-2 HCAPLUS

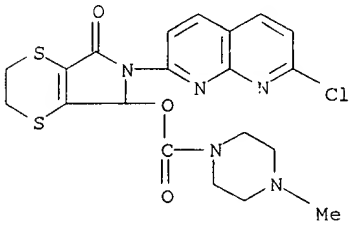
CN 1-Piperazinecarboxylic acid, 4-methyl-, 6-(5-chloro-2-pyridinyl)-6,7-dihydro-7-oxo-5H-pyrrolo[3,4-b]pyrazin-5-yl ester (9CI) (CA INDEX NAME)



IT **53813-83-5**, Suriclone
RL: BIOL (Biological study)
(receptor binding by, structure in relation to)

RN 53813-83-5 HCAPLUS

CN 1-Piperazinecarboxylic acid, 4-methyl-, 6-(7-chloro-1,8-naphthyridin-2-yl)-2,3,6,7-tetrahydro-7-oxo-5H-1,4-dithiino[2,3-c]pyrrol-5-yl ester (9CI) (CA INDEX NAME)



L34 ANSWER 37 OF 55 HCAPLUS COPYRIGHT 2000 ACS

AN 1986:546045 HCAPLUS

DN 105:146045

TI Pharmacological studies on stress-induced increase in frontal cortical dopamine metabolism in the rat

AU Claustre, Yves; Rivy, Jean Paul; Dennis, Trevor; Scatton, Bernard

CS Lab. Etud. Rech. Synth., Bagneux, 92220, Fr.

SO J. Pharmacol. Exp. Ther. (1986), 238(2), 693-700
CODEN: JPETAB; ISSN: 0022-3565

DT Journal

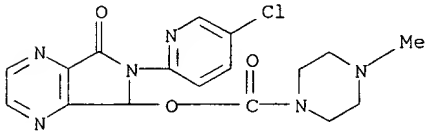
LA English

AB The effects of a variety of minor tranquilizers and of benzodiazepine inverse agonists on the stress-induced increase in frontal cortical dopamine [51-61-6] metab. were studied in the rat. Elec. footshock stress increased 3,4-dihydroxyphenylacetic acid (DOPAC) [102-32-9] levels in the frontal (but not parietal) cortex and in the nucleus accumbens but not in the striatum or ventral tegmental area. Similar stress-induced alterations of frontal cortical DOPAC levels were obsd. after DSP4-induced noradrenergic denervation or after adrenalectomy. Other types of stress, e.g., conditioned fear (exposure to an environment paired previously with footshock) or swim stress also provoked an elevation of DOPAC levels in the prefrontal cortex. When administered systemically, the anxiolytic agents meprobamate [57-53-4], CL 218872 [66548-69-4], CGS 9896 [77779-36-3], and suriclone [**53813-83-5**] and the hypnotic/anxiolytic drugs zolpidem [82626-48-0] and zopiclone [**43200-80-2**] all prevented the elec. footshock stress-induced augmentation of cortical DOPAC levels, whereas the **GABA receptor** agonists progabide [62666-20-0], muscimol [2763-96-4] and depamide [2430-27-5] or the sedative .alpha.1-adrenoceptor antagonist prazosin [19216-56-9] were ineffective. The preventive effect of

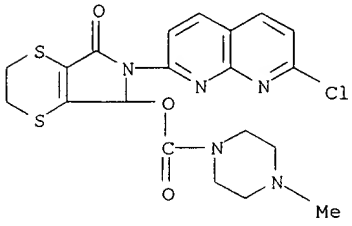
diazepam [439-14-5] and zolpidem on the stress-induced biochem. response was antagonized by the benzodiazepine antagonist CGS 8216 [77779-60-3] but not by the **GABA receptor** antagonist (.+-.)-bicuculline [56083-00-2]. In nonstressed rats, systemic administration of the anxiogenic benzodiazepine inverse agonists .beta.-CCM (Me .beta.-carboline-3-carboxylate) [69954-48-9] and .beta.-CCE (Et .beta.-carboline-3-carboxylate) [74214-62-3], but not of the benzodiazepine antagonists Ro 15-1788 [78755-81-4] or CGS 8216, caused an increase in frontal cortical DOPAC similar to that provoked by stress and which was antagonized by zolpidem. Finally, local injection of zolpidem (up to 10 .mu.g) into the prefrontal cortex or into the ventral tegmental area failed to prevent the footshock stress-induced increase in frontal cortical DOPAC levels. It is concluded that (with the exception of meprobamate) minor tranquilizers antagonize stress-induced increase in frontal cortical dopamine metab. via interaction with benzodiazepine receptors, this effect likely being related to the anxiolytic properties of these drugs. The effect of minor tranquilizers does not appear to be related to a direct action on dopaminergic neurons. The fact that benzodiazepine inverse agonists activate frontal cortical dopamine metab. as does stress adds further support to the view that the mesoprefrontal dopaminergic system is involved in emotional behavior.

IT **43200-80-2 53813-83-5**
RL: BIOL (Biological study)
(stress-induced frontal cortex dopamine metab. increase prevention by)

RN 43200-80-2 HCAPLUS
CN 1-Piperazinecarboxylic acid, 4-methyl-, 6-(5-chloro-2-pyridinyl)-6,7-dihydro-7-oxo-5H-pyrrolo[3,4-b]pyrazin-5-yl ester (9CI) (CA INDEX NAME)



RN 53813-83-5 HCAPLUS
CN 1-Piperazinecarboxylic acid, 4-methyl-, 6-(7-chloro-1,8-naphthyridin-2-yl)-2,3,6,7-tetrahydro-7-oxo-5H-1,4-dithiino[2,3-c]pyrrol-5-yl ester (9CI) (CA INDEX NAME)



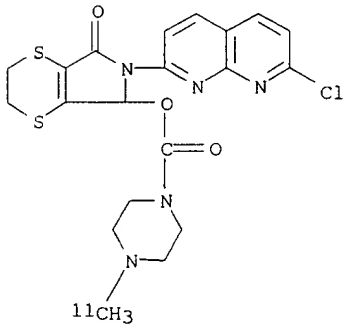
L34 ANSWER 38 OF 55 HCAPLUS COPYRIGHT 2000 ACS
AN 1986:457087 HCAPLUS
DN 105:57087
TI Imaging benzodiazepine receptors in man with [11C]suriclone by positron emission tomography
AU Frost, J. James; Wagner, Henry N., Jr.; Dannals, Robert F.; Ravert, Hayden T.; Wilson, Alan A.; Links, Jonathan M.; Rosenbaum, Arthur E.; Trifiletti, Rosario R.; Snyder, Solomon H.
CS Dep. Neurosci., Johns Hopkins Med. Inst., Baltimore, MD, 21205, USA
SO Eur. J. Pharmacol. (1986), 122(3), 381-3
CODEN: EJPHAZ; ISSN: 0014-2999
DT Journal
LA English
AB Position emission tomog. of brain benzodiazepine receptors was performed

in baboons and man by using [11C]suriclone. In baboons, radioactivity was most intense in the cerebellum and cerebral cortex and negligible in the caudate nucleus, consistent with the known distribution of benzodiazepine-**GABA receptors**. Humans showed a similar distribution, with slow dissocn. of [11C]suriclone from receptors 3-72 min postadministration. The results indicate that [11C]suriclone is an excellent agent for imaging benzodiazepine-**GABA receptors**.

IT **103424-67-5**
RL: BIOL (Biological study)
(positron emission tomog. with, of benzodiazepine receptors of brain of baboons and human)

RN 103424-67-5 HCAPLUS

CN 1-Piperazinecarboxylic acid, 4-(methyl-11C)-, 6-(7-chloro-1,8-naphthyridin-2-yl)-2,3,6,7-tetrahydro-7-oxo-5H-1,4-dithiino[2,3-c]pyrrol-5-yl ester (9CI) (CA INDEX NAME)



L34 ANSWER 39 OF 55 HCAPLUS COPYRIGHT 2000 ACS

AN 1986:400503 HCAPLUS

DN 105:503

TI Neuroanatomical site of the inhibitory influence of anxiolytic drugs on central serotonergic transmission

AU Nishikawa, Toru; Scatton, Bernard

CS Biochem. Group, Lab. Etud. Rech. Synthelabo, Bagneux, 92220, Fr.

SO Brain Res. (1986), 371(1), 123-32
CODEN: BRREAP; ISSN: 0006-8993

DT Journal

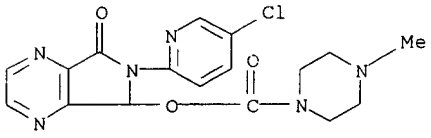
LA English

AB The neuroanatomical site of the inhibitory influence of anxiolytics on central serotonergic transmission was investigated in the rat by studying the effect of systemic or intracerebral administration of these drugs on cerebral serotonin (5-HT) [50-67-9] synthesis. Systemic administration of diazepam [439-14-5] (3 mg/kg, s.c.) or flunitrazepam [1622-62-4] (1 mg/kg, s.c.) caused a redn. of 5-HT synthesis (as measured by the accumulation of 5-hydroxytryptophan after inhibition of arom. amino acid decarboxylase [9042-64-2]) in the hippocampus but not in the cerebral cortex, striatum, cerebellum or spinal cord of the rat. Zopiclone [**43200-80-2**] (22 mg/kg, s.c.) decreased the amine synthesis in hippocampus, striatum and prefrontal cortex. The decrease of hippocampal 5-HT synthesis induced by diazepam (5 mg/kg, s.c.) was antagonized by the benzodiazepine antagonist Ro 15-1788 (2 .times. 30 mg/kg, s.c.) but not by the **GABA receptor** antagonist bicuculline (2 .times. 1 mg/kg, s.c.). Acute cerebral hemitransection or electrolytic lesion of the fasciculus retroflexus did not prevent the ability of diazepam (5 mg/kg, i.p.) to diminish hippocampal 5-HT synthesis. Local infusion of diazepam (15 .mu.g) of flurazepam (1.5 .mu.g) into the hippocampus of conscious rats (via indwelling cannulae) markedly reduced 5-HT synthesis in this brain area whereas infusion of these drugs into the raphe medianus (origin of the serotonergic afferents to the hippocampus) failed to affect hippocampal 5-HT synthesis. In contrast, local injection of muscimol [2763-96-4] (25-150 ng) into the raphe medianus reduced 5-HT synthesis in the hippocampus. This effect of muscimol was potentiated by a systematic

administration of diazepam or an intra-raphe medianus infusion of flurazepam (at doses or concns. which exhibited no intrinsic activity). It is concluded from these data that anxiolytic drugs exert an inhibitory influence on hippocampal serotonergic neurons which is mediated primarily via **GABA**-independent benzodiazepine **receptors** located in the vicinity of serotonergic nerve terminals.

IT **43200-80-2**
RL: BIOL (Biological study)
(serotonin formation by brain regions response to)

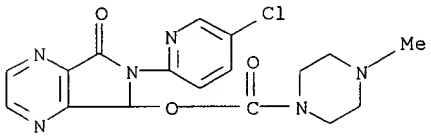
RN 43200-80-2 HCAPLUS
CN 1-Piperazinecarboxylic acid, 4-methyl-, 6-(5-chloro-2-pyridinyl)-6,7-dihydro-7-oxo-5H-pyrrolo[3,4-b]pyrazin-5-yl ester (9CI) (CA INDEX NAME)



L34 ANSWER 40 OF 55 HCAPLUS COPYRIGHT 2000 ACS
AN 1985:553978 HCAPLUS
DN 103:153978
TI Effects of GABA and benzodiazepine antagonists on anticonflict actions of anxiolytics in a water-lick conflict procedure in rats
AU Ozaki, Toru; Shibata, Shigenoba; Shibata, Kazuhiko; Ueki, Showa
CS Pharm. Coll., Kyushu Univ., Fukuoka, Japan
SO Yakubutsu, Seishin, Kodo (1985), 5(2), 205-6
CODEN: YSKODB; ISSN: 0285-5313
DT Journal
LA Japanese
AB Conflict behavior measured by the water-lick conflict method in rats was inhibited by anxiolytics such as diazepam [439-14-5], zopiclone [**43200-80-2**], and phenobarbital [50-06-6]. The inhibition by diazepam and zopiclone was antagonized by Ro 151788 and .beta.-CCM (benzodiazepine antagonists). It is apparently mediated by benzodiazepine receptors. However, the inhibition by phenobarbital was not influenced by Ro 151788 or .beta.-CCM. The anticonflict activity of the anxiolytics was not antagonized by the **GABA receptor** antagonist bicuculline.

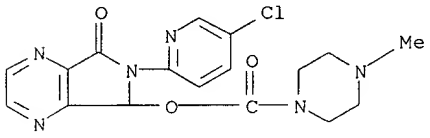
IT **43200-80-2**
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(anxiolytic activity of, **GABA** and benzodiazepine **receptors** in brain in relation to)

RN 43200-80-2 HCAPLUS
CN 1-Piperazinecarboxylic acid, 4-methyl-, 6-(5-chloro-2-pyridinyl)-6,7-dihydro-7-oxo-5H-pyrrolo[3,4-b]pyrazin-5-yl ester (9CI) (CA INDEX NAME)



L34 ANSWER 41 OF 55 HCAPLUS COPYRIGHT 2000 ACS
AN 1985:535094 HCAPLUS
DN 103:135094
TI Benzodiazepine-induced hyperphagia in the nondeprived rat: comparisons with CL 218,872, zopiclone, tracazolate and phenobarbital
AU Cooper, Steven J.; Moores, William R.
CS Dep. Psychol., Univ. Birmingham, Birmingham, B15 2TT, UK
SO Pharmacol., Biochem. Behav. (1985), 23(2), 169-72

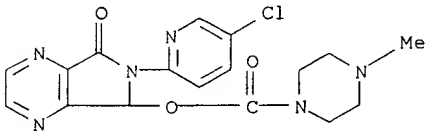
CODEN: PBBHAU; ISSN: 0091-3057
DT Journal
LA English
AB Nondeprived male rats were familiarized with 30 min daily access to a highly palatable diet. Clonazepam [1622-61-3], midazolam bimaleate [59467-94-6], and chlordiazepoxide [58-25-3] each produced significant dose-dependent increases in food consumption. Clonazepam was the most potent, and a significant hyperphagic effect was detected following 0.078 mg/kg (i.p.). Amongst novel non-benzodiazepine anxiolytics, zopiclone [**43200-80-2**] and CL 218,872 [66548-69-4] also produced significant increases in food intake. The smallest doses to produce significant hyperphagia for these 2 drugs were 10.0 and 2.5 mg/kg (i.p.) resp. In contrast, tracazolate [41094-88-6] cause only a redn. in feeding, evident at 20 and 40 mg/kg (i.p.). Previous reports indicate that although benzodiazepines, zopiclone and CL 218,872 displace [3H]flunitrazepam binding in rat cerebral cortex prepns., tracazolate enhances the binding. These results are consistent with the drug-induced hyperphagia depending upon agonist actions at high-affinity benzodiazepine sites. They also provide pharmacol. evidence for a dissocn. between hyperphagic and anxiolytic drug effects. Phenobarbital [50-06-6] (2.5-40.0 mg/kg), like the benzodiazepines, produced a strong stimulation of food intake, indicating that drug action at an alternative site in the benzodiazepine **receptor**-**GABA** **receptor**-chloride channel complex can also lead to hyperphagia.
IT **43200-80-2**
RL: BIOL (Biological study)
(hyperphagia induced by, benzodiazepine receptor in relation to)
RN 43200-80-2 HCAPLUS
CN 1-Piperazinecarboxylic acid, 4-methyl-, 6-(5-chloro-2-pyridinyl)-6,7-dihydro-7-oxo-5H-pyrrolo[3,4-b]pyrazin-5-yl ester (9CI) (CA INDEX NAME)



L34 ANSWER 42 OF 55 HCAPLUS COPYRIGHT 2000 ACS
AN 1985:90448 HCAPLUS
DN 102:90448
TI Modulation of acetylcholine release from rat striatal slices by the **GABA**/benzodiazepine **receptor** complex
AU Supavilai, Porntip; Karobath, Manfred
CS Preclin. Res., Sandoz Ltd., Basle, CH-4002, Switz.
SO Life Sci. (1985), 36(5), 417-26
CODEN: LIFSAK; ISSN: 0024-3205
DT Journal
LA English
AB GABA [56-12-2], THIP [64603-91-4], and muscimol [2763-96-4] enhanced spontaneous and inhibited elec. induced release of 3H-labeled compds. from rat striatal slices which had been pre-labeled with [3H]-choline. Baclofen was inactive in this model. Muscimol inhibited elec. induced release of 3H by .apprx.75% with half maximal effects at 2 .mu.M. The response to muscimol was blocked by the GABA antagonists bicuculline methobromide, picrotoxin, anisatin, R 5135, and cyclopentylbicyclophoshate. Drugs which act on the benzodiazepine receptor (BR) required the presence of muscimol to be effective and they modulated the effects of muscimol in a bidirectional manner. Thus BR agonists enhanced and inverse BR agonists attenuated the inhibitory effects of muscimol on elec. induced release. Ro15-1788, a BR antagonist, did not modulate the inhibitory effects of muscimol but antagonized the actions of clonazepam [1622-61-3], a BR agonist, and of DMCM [82499-00-1], an inverse BR agonist. Apparently a **GABA** /benzodiazepine **receptor** complex can modulate acetylcholine [51-84-3] release from rat striatal slices in vitro.
IT **43200-80-2**

RL: BIOL (Biological study)
(acetylcholine release by striatum response to, **GABAergic receptors** in relation to)

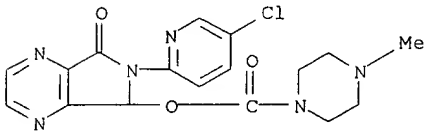
RN 43200-80-2 HCAPLUS
CN 1-Piperazinecarboxylic acid, 4-methyl-, 6-(5-chloro-2-pyridinyl)-6,7-dihydro-7-oxo-5H-pyrrolo[3,4-b]pyrazin-5-yl ester (9CI) (CA INDEX NAME)



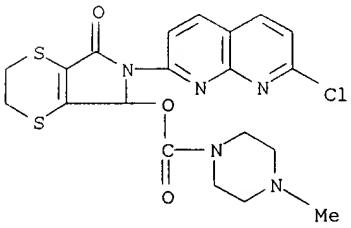
L34 ANSWER 43 OF 55 HCAPLUS COPYRIGHT 2000 ACS
AN 1985:55570 HCAPLUS
DN 102:55570
TI Anxiolytic cyclopyrrolone drugs allosterically modulate the binding of [35S]t-butylbicyclophosphorothionate to the benzodiazepine/.**gamma**.-**aminobutyric acid**-A **receptor**/chloride anionophore complex
AU Trifiletti, Rosario R.; Snowman, Adele M.; Snyder, Solomon H.
CS Sch. Med., Johns Hopkins Univ., Baltimore, MD, 21205, USA
SO Mol. Pharmacol. (1984), 26(3), 470-6
CODEN: MOPMA3; ISSN: 0026-895X
DT Journal
LA English
AB The influence of a no. of anxiolytic cyclopyrrolone drugs, which include zopiclone [**43200-80-2**] and suriclone [**53813-83-5**], on the binding of 35S-labeled t-butylbicyclophosphorothionate (TBPS) [70636-86-1] to benzodiazepine/.**gamma**.-**aminobutyric acid**-A **receptor**/chloride anionophore complexes has been characterized in rat brain. Suriclone and its metabolites RP35,489 [**94342-72-0**] and RP46,166 [**94342-73-1**] are the most potent (IC50 .apprx. 3nM) inhibitors of [35S]TBPS binding thus far described, about an order of magnitude more potent than TBPS itself. The pattern of inhibition of [35S]TBPS binding by suriclone is distinctive; at .apprx.10 nM there is approx. 50% inhibition of [35S]TBPS binding and inhibition "plateaus" at this level until suriclone concns. exceed 1 .mu.M. RP35,489 and RP46,166 display patterns of inhibition similar to suriclone. In satn. studies of [35S]TBPS binding, suriclone reduces the Bmax of [35S]TBPS-binding sites, with little or no effect on KD. Muscimol [2763-96-4] also displays a noncompetitive pattern of inhibition of [35S]TBPS binding, whereas inhibition by picrotoxinin [17617-45-7] appears competitive. [35S]TBPS dissocn. is multiphasic and similar whether initiated by 10 .mu.M TBPS or 10 .mu.M picrotoxinin. By contrast, dissocn. of [35S]TBPS is much faster (and nearly monophasic) when initiated by 10 .mu.M TBPS/100 nM suriclone, 10 .mu.M TBPS/1 .mu.M muscimol, or 10 .mu.M TBPS/1 mM pentobarbital [76-74-4]. Apparently, suriclone influences [35S]TBPS binding allosterically at sites distinct from the TBPS/picrotoxinin recognition site. Inhibition of [35S]TBPS binding by suriclone varies regionally with a "plateau" at .apprx.20% inhibition in the cerebellum, .apprx.50% in the cerebral cortex, hippocampus and brain stem, and .apprx.65% in the striatum and midbrain; by contrast, inhibition of [35S]TBPS by picrotoxinin, muscimol, and pentobarbital shows little regional variation. The inhibition of [35S]TBPS binding by suriclone is reversed by bicuculline [485-49-4] [ED50 .apprx.1 .mu.M] in several brain regions examd. Bicuculline alone has little or no influence on [35S]TBPS binding in the cerebral cortex, hippocampus, and cerebellum, but produces a dose-dependent enhancement of [35S]TBPS binding in the striatum, midbrain, and hypothalamus. Regional differences in the effects of suriclone and bicuculline on [35S]TBPS recognition sites suggest possible heterogeneity in the coupling of cyclopyrrolone and bicuculline recognition sites to [35S]TBPS recognition sites in rat brain.
IT **43200-80-2 53813-83-5 59878-27-2 94342-73-1**

RL: BIOL (Biological study)
(butylbicyclophosphorothionate binding to brain benzodiazepine-**GABA receptor** complex response to)

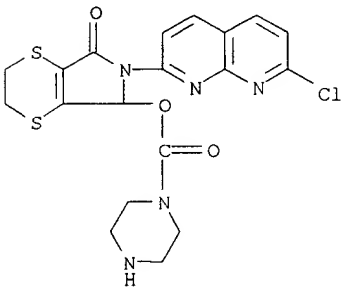
RN 43200-80-2 HCAPLUS
CN 1-Piperazinecarboxylic acid, 4-methyl-, 6-(5-chloro-2-pyridinyl)-6,7-dihydro-7-oxo-5H-pyrrolo[3,4-b]pyrazin-5-yl ester (9CI) (CA INDEX NAME)



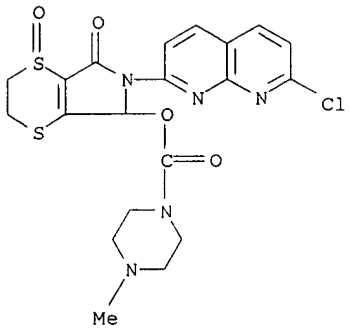
RN 53813-83-5 HCAPLUS
CN 1-Piperazinecarboxylic acid, 4-methyl-, 6-(7-chloro-1,8-naphthyridin-2-yl)-2,3,6,7-tetrahydro-7-oxo-5H-1,4-dithiino[2,3-c]pyrrol-5-yl ester (9CI) (CA INDEX NAME)



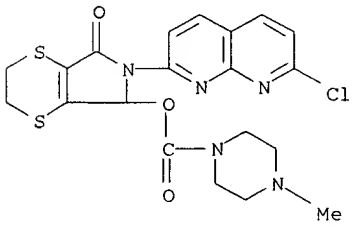
RN 59878-27-2 HCAPLUS
CN 1-Piperazinecarboxylic acid, 6-(7-chloro-1,8-naphthyridin-2-yl)-2,3,6,7-tetrahydro-7-oxo-5H-1,4-dithiino[2,3-c]pyrrol-5-yl ester (9CI) (CA INDEX NAME)



RN 94342-73-1 HCAPLUS
CN 1-Piperazinecarboxylic acid, 4-methyl-, 6-(7-chloro-1,8-naphthyridin-2-yl)-2,3,6,7-tetrahydro-1-oxido-7-oxo-5H-1,4-dithiino[2,3-c]pyrrol-5-yl ester (9CI) (CA INDEX NAME)

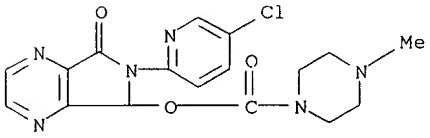


L34 ANSWER 44 OF 55 HCAPLUS COPYRIGHT 2000 ACS
AN 1984:583945 HCAPLUS
DN 101:183945
TI Suriclone, a new anxiolytic of the cyclopyrrolone family: evidence for possible interference with GABAergic systems
AU Boireau, Alain; Stutzmann, Jean Marie; Garret, Claude; Julou, Louis; Blanchard, Jean Charles
CS Cent. Rech. Vitry, Rhone-Poulenc Sante, Vitry sur Seine, 94407, Fr.
SO Eur. J. Pharmacol. (1984), 104(1-2), 139-44
CODEN: EJPHAZ; ISSN: 0014-2999
DT Journal
LA English
AB The action of suriclone (R.P. 31,264) [**53813-83-5**] was examd. using biochem. and electrophysiol. models capable of revealing central GABAergic activity. Suriclone, which does not act directly on the **GABA** [56-12-2] **receptor** (muscimol binding assay, markedly reduced the increase of striatal homovanilic acid [306-08-1] induced in the rat by a neuroleptic and decreased the cerebellar vermis cGMP [7665-99-8] content. Moreover, in the cat, suriclone enhanced dorsal root potential amplitude which reflects an increase of the presynaptic inhibition. In view of these results, a central GABAergic mechanism of action may be proposed for suriclone.
IT **53813-83-5**
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(GABAergic system of brain response to)
RN 53813-83-5 HCAPLUS
CN 1-Piperazinecarboxylic acid, 4-methyl-, 6-(7-chloro-1,8-naphthyridin-2-yl)-2,3,6,7-tetrahydro-7-oxo-5H-1,4-dithiino[2,3-c]pyrrol-5-yl ester (9CI) (CA INDEX NAME)

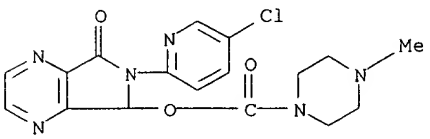


L34 ANSWER 45 OF 55 HCAPLUS COPYRIGHT 2000 ACS
AN 1984:583832 HCAPLUS
DN 101:183832
TI Bidirectional effects on anxiety of .beta.-carbolines acting as benzodiazepine receptor ligands
AU Stephens, D. N.; Kehr, W.; Schneider, H. H.; Braestrup, C.
CS Res. Lab., Schering A.-G., Berlin, Fed. Rep. Ger.

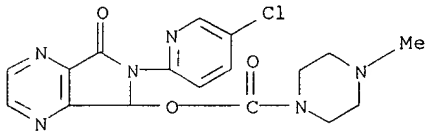
SO Neuropharmacology (1984), 23(7B), 879-80
CODEN: NEPHBW; ISSN: 0028-3908
DT Journal
LA English
AB Although the antipunishment activity of anxiolytic benzodiazepine (BZ) receptor ligands correlated with their binding potency in vivo, certain .beta.-carboline ligands enhanced the punishing effects of footshock and antagonized diazepam [439-14-5]'s antipunishment action. Similar bidirectional effects were seen in rats trained to discriminate between pentylenetetrazol (PTZ) and saline injections to obtain food in an operant task. BZ-like .beta.-carbolines antagonized the PTZ cue whereas those with propunishment properties substituted for it. The direction of the effect of .beta.-carbolines depended on whether they enhanced (anxiolytic) or inhibited binding of [35S]-t-butylbicyclophosphorothionate to the **GABA**/BZ-**receptor**/Cl ionophore complex.
IT **43200-80-2**
RL: BIOL (Biological study)
(anxiety response to, benzodiazepine receptor affinity in relation to)
RN 43200-80-2 HCAPLUS
CN 1-Piperazinecarboxylic acid, 4-methyl-, 6-(5-chloro-2-pyridinyl)-6,7-dihydro-7-oxo-5H-pyrrolo[3,4-b]pyrazin-5-yl ester (9CI) (CA INDEX NAME)



L34 ANSWER 46 OF 55 HCAPLUS COPYRIGHT 2000 ACS
AN 1984:483849 HCAPLUS
DN 101:83849
TI Benzodiazepine receptor ligands, **receptor** occupancy, pharmacological effect and **GABA receptor** coupling
AU Braestrup, C.; Schmiechen, R.; Nielsen, M.; Petersen, E. N.
CS Psychopharmacol. Res. Lab., St Hans Ment. Hosp., Roskilde, DK-4000, Den.
SO Pharmacol. Benzodiazepines, Proc. Conf. (1983), Meeting Date 1982, 71-85. Editor(s): Usdin, Earl. Publisher: Verlag Chem., Weinheim, Fed. Rep. Ger.
CODEN: 52AKA7
DT Conference
LA English
AB The relation between the receptor binding of benzodiazepine receptor ligands and their pharmacol. activity was detd. The apparent failure of some unconventional benzodiazepine ligands to elicit benzodiazepine pharmacol. effects could not be explained by a failure to occupy in vivo any of the known benzodiazepine receptor subclasses. These agents bound to benzodiazepine receptors in a way different from conventional benzodiazepines, probably inducing distinct conformational changes in the benzodiazepine **receptor** that might reduce **GABAergic** neurotransmission. In particular, this seems to be the case for methyl-6,7-dimethoxy-4-ethyl-.beta.-carboline-3-carboxylate [82499-00-1], a new convulsive benzodiazepine receptor ligand.
IT **43200-80-2**
RL: BIOL (Biological study)
(benzodiazepine receptor binding and pharmacol. of)
RN 43200-80-2 HCAPLUS
CN 1-Piperazinecarboxylic acid, 4-methyl-, 6-(5-chloro-2-pyridinyl)-6,7-dihydro-7-oxo-5H-pyrrolo[3,4-b]pyrazin-5-yl ester (9CI) (CA INDEX NAME)



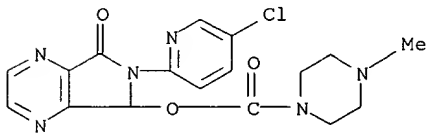
L34 ANSWER 47 OF 55 HCAPLUS COPYRIGHT 2000 ACS
AN 1984:448576 HCAPLUS
DN 101:48576
TI Benzodiazepine **receptor** ligand actions on **GABA** responses. Benzodiazepines, CL 218872, zopiclone
AU Skerritt, John H.; MacDonald, Robert L.
CS Dep. Neurol., Univ. Michigan, Ann Arbor, MI, 48109, USA
SO Eur. J. Pharmacol. (1984), 101(1-2), 127-34
CODEN: EJPHAZ; ISSN: 0014-2999
DT Journal
LA English
AB The effects on GABA [56-12-2] responses of several benzodiazepine and nonbenzodiazepine benzodiazepine receptor ligands were examd. using mouse spinal cord neurons in dissocd. cell culture. Diazepam [439-14-5], clonazepam [1622-61-3], and nitrazepam [146-22-5] enhanced GABA responses potently at low-nanomolar concns. Diazepam and clonazepam were most potent with significant enhancement at 1 nM and peak enhancement of 80.7 and 50.2% at 10 nM, resp. Nitrazepam was least potent with no significant enhancement at 1 nM and enhancement of only 20.7% at 10 nM. The benzodiazepine antagonist, Ro 15-1788 [78755-81-4], blocked enhancement by diazepam but also weakly enhanced GABA responses at low micromolar concns., suggesting partial agonist activity. The convulsant benzodiazepine, Ro 5-4864 [14439-61-3], did not enhance GABA responses at any concn. tested but antagonized GABA responses at 1 .mu.M and above. Diazepam shifted GABA dose-response curves to the left by decreasing the apparent KD but without altering the apparent Vmax (Lineweaver-Burk anal.). Two nonbenzodiazepine anxiolytic-anticonvulsants, CL 218872 [66548-69-4] and zopiclone [**43200-80-2**], were weak enhancers of GABA responses at high-nanomolar concns. These results with benzodiazepines, CL 218872 and zopiclone are consistent with their anxiolytic and anticonvulsant profile in vivo and with studies of their effects upon low affinity GABA binding in vitro.
IT **43200-80-2**
RL: BIOL (Biological study)
(GABA neurotransmission in spinal cord neurons response to)
RN 43200-80-2 HCAPLUS
CN 1-Piperazinecarboxylic acid, 4-methyl-, 6-(5-chloro-2-pyridinyl)-6,7-dihydro-7-oxo-5H-pyrrolo[3,4-b]pyrazin-5-yl ester (9CI) (CA INDEX NAME)



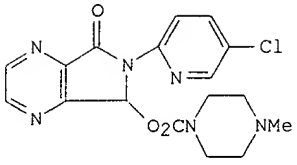
L34 ANSWER 48 OF 55 HCAPLUS COPYRIGHT 2000 ACS
AN 1984:417266 HCAPLUS
DN 101:17266
TI [35S]-tert-Butylbicyclophosphorothionate binding sites are constituents of the .**gamma.-aminobutyric acid** benzodiazepine **receptor** complex
AU Supavilai, Porntip; Karobath, Manfred
CS Sandoz Ltd., Basel, CH-4002, Switz.
SO J. Neurosci. (1984), 4(5), 1193-200
CODEN: JNRSDS; ISSN: 0270-6474
DT Journal
LA English
AB In the presence of 200 mM NaBr, [35S]T35S-labeled t-butylbicyclophosphorothionate (TBPS) [70636-86-1] binds to a high-affinity population of binding sites (Kd 26 nM) in rat cerebral cortex, and muscimol inhibits [35S]TBPS binding (IC50 0.32 .mu.M) allosterically. In 200-mM NaCl the apparent affinity of [35S]TBPS binding sites is lower (Kd 60 nM), and muscimol has biphasic effects with stimulation at low concns. of muscimol (EC50 0.023 .mu.M) followed by

inhibition at high concns. (IC50 0.72 .mu.M). Both base-line [35S]TBPS binding (in 200-mM NaCl) and muscimol inhibition of [35S]TBPS binding (in 200-mM NaBr) are bidirectionally modulated by the occupancy of benzodiazepine receptors with its ligands. Benzodiazepine-receptor agonists, regardless of their structure, enhance, and inverse benzodiazepine-receptor agonists inhibit base-line [35S]TBPS binding and muscimol inhibition of [35S]TBPS binding. Fourteen ligands for benzodiazepine receptors display a similar in vitro profile as benzodiazepine-receptor agonists or inverse benzodiazepine-receptor agonists on [35S]TBPS binding, as their anti- or proconvulsive effects in vivo suggest. That [35S]TBPS binding sites are constituents of a **GABA**-benzodiazepine-**receptor** complex is also suggested by a no. of membrane pretreatments. After photoaffinity-labeling of benzodiazepine receptors with flunitrazepam [1622-62-4], [35S]TBPS binding sites became insensitive to modulation by flunitrazepam but not by 6,7-dimethoxy-4-ethyl-.beta.-carboline-3-carboxylic acid Me ester [82499-00-1]. Pretreatment of membranes with Ag+ ions (which leads to the sole appearance of high-affinity [3H]muscimol binding sites, to high-affinity muscimol stimulation of [3H]flunitrazepam binding, and to a loss of allosteric modulation of these binding sites by etazolate (SQ 20009) [51022-77-6] or isopropylbicyclophosphate (IPTBO) [51052-72-3]), results in the disappearance of [35S]TBPS binding. Pretreatment of membranes with Triton S-100, which perturbs the **GABA**- and benzodiazepine-**receptor** binding in a mode similar to Ag+ ions, also leads to the disappearance of [35S]TBPS binding. Thus [35S]TAbPS binding sites can be inactivated sep. from **GABA**- and benzodiazepine-**receptors**, and this inactivation goes parallel with perturbation of **GABA** and benzodiazepine **receptor** binding. The CNS depressants etazolate and pentobarbital [76-74-4] differ in their effects on [35S]TBPS binding as compared with picrotoxinin and IPTBO. The latter compds. inhibit [35S]TBPS binding unperturbed by the occupancy of benzodiazepine receptors. Etazolate and pentobarbital (in 200-mM NaCl) have biphasic effects on [35S]TBPS binding with stimulation at low concns. (EC50 0.4 .mu.M and 60.4 .mu.M) and inhibition (IC50 12.9 .mu.M and 550 .mu.M) at higher concns., with Hill nos. of 1.5 and 2.7. The potencies of etazolate or pentobarbital as inhibitors of [35S]TBPS binding (in 200-mM NaBr) are bidirectionally modulated by the occupancy of benzodiazepine receptors with agonists or with inverse agonists. These observations are not compatible with the concept that these CNS depressants and CNS convulsants act on an identical drug receptor.

IT **43200-80-2**
RL: BIOL (Biological study)
(butylbicyclophosphorothionate binding by brain response to, **GABA**-benzodiazepine-**receptor** complex in relation to)
RN 43200-80-2 HCAPLUS
CN 1-Piperazinecarboxylic acid, 4-methyl-, 6-(5-chloro-2-pyridinyl)-6,7-dihydro-7-oxo-5H-pyrrolo[3,4-b]pyrazin-5-yl ester (9CI) (CA INDEX NAME)



L34 ANSWER 49 OF 55 HCAPLUS COPYRIGHT 2000 ACS
AN 1984:185638 HCAPLUS
DN 100:185638
TI Brain receptors and zopiclone
AU Blanchard, J. C.; Boireau, A.; Julou, L.
CS Cent. Nicolas Grillet, Rhone-Poulenc Rech., Vitry-sur-Seine, Fr.
SO Int. Pharmacopsychiatry (1983), Volume Date 1982, 17(Suppl. 2), 59-69
CODEN: INPHB6; ISSN: 0020-8272
DT Journal
LA English
GI



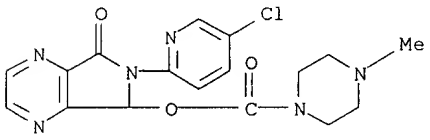
I

AB Zopiclone (I) [**43200-80-2**] displaced [3H]flunitrazepam from high-affinity benzodiazepine (BZD) receptors in 3 different rat brain areas (Ki = 24 nM, 31 nM, and 36 nM for the cerebral cortex, cerebellum, and hippocampus, resp.). This interaction was confirmed with [3H]I binding which was also of high affinity (KD = 13 nM in the hippocampus). I, however, did not bind to dopaminergic, **GABAergic**, serotoninergic, or noradrenergic **receptors** in the brain. I also did not bind to peripheral BZD receptors in the kidney. Several other differences in the behavior of I and flunitrazepam binding to brain were obsd. Thus, I may interact with sites other than BZD receptors in the brain.

IT **43200-80-2**
RL: PROC (Process)
(binding of, to benzodiazepine receptors)

RN 43200-80-2 HCAPLUS

CN 1-Piperazinecarboxylic acid, 4-methyl-, 6-(5-chloro-2-pyridinyl)-6,7-dihydro-7-oxo-5H-pyrrolo[3,4-b]pyrazin-5-yl ester (9CI) (CA INDEX NAME)



L34 ANSWER 50 OF 55 HCAPLUS COPYRIGHT 2000 ACS

AN 1984:168086 HCAPLUS

DN 100:168086

TI Effect of GABA and photoaffinity labeling on the affinity of drugs for benzodiazepine receptors in membranes of the cerebral cortex of five-day-old rats

AU Borea, Pier Andrea; Supavilai, Porntip; Karobath, Manfred

CS Preclin. Res., Sandoz Ltd., Basel, Switz.

SO Biochem. Pharmacol. (1984), 33(1), 165-8
CODEN: BCPCA6; ISSN: 0006-2952

DT Journal

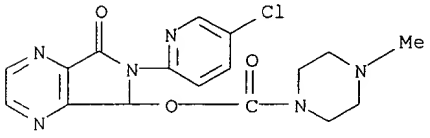
LA English

AB Satn.-equil. binding studies in membranes from the cerebral cortex of 5-day-old rats showed that flunitrazepam [1622-62-4] and Ro-15-1788 [78755-81-4] label approx. the same no. of binding sites, whereas ethyl-.beta.-carboline-3-carboxylate (I) [74214-62-3] bound to fewer sites, showing that the young cortex contains significant amts. of benzodiazepine receptors which are not type I. GABA [56-12-2] (10 .mu.M) markedly inhibited I binding, in contrast to the case with adult cortex. Moreover, photoaffinity labeling of the binding sites did not impair the interaction between GABA-recognition sites and the other benzodiazepine binding sites of **GABA**-benzodiazepine **receptor** complex. Studies with other drugs showed that GABA enhances the apparent affinity of drugs with benzodiazepine-like effects, but decreases that of the partial inverse agonists CGC 8216 [77779-60-3], I, and methyl-.beta.-carboline-3-carboxylate [69954-48-9]. The magnitude of the GABA-induced affinity changes is similar in membranes previously photoaffinity-labeled with flunitrazepam, and the affinity of

benzodiazepines for their binding sites is greatly decreased in photoaffinity-labeled membranes. Binding sites populated by I exhibit similar sensitivity to modulation by GABA and photoaffinity labeling as do those labeled by Ro-15-1788.

IT **43200-80-2**
RL: PRP (Properties)
(affinity of, for benzodiazepine **receptor** of cortex, **GABA** and photoaffinity labeling of **receptor** effect on)

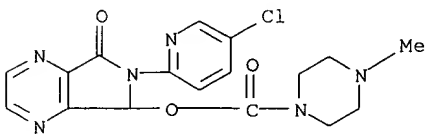
RN 43200-80-2 HCAPLUS
CN 1-Piperazinecarboxylic acid, 4-methyl-, 6-(5-chloro-2-pyridinyl)-6,7-dihydro-7-oxo-5H-pyrrolo[3,4-b]pyrazin-5-yl ester (9CI) (CA INDEX NAME)



L34 ANSWER 51 OF 55 HCAPLUS COPYRIGHT 2000 ACS
AN 1984:96664 HCAPLUS
DN 100:96664
TI Brain receptors and zopiclone
AU Blanchard, J. C.; Boireau, A.; Julou, L.
CS Cent. Nicolas Grillet, Rhone-Poulenc Rech., Vitry-sur-Seine, F-94400, Fr.
SO Pharmacology (1983), 27(Suppl. 2), 59-69
CODEN: PHMGBN; ISSN: 0031-7012
DT Journal
LA English
AB Zopiclone (ZPC) [**43200-80-2**], chem. unrelated to benzodiazepines (BZD), has a similar pharmacol. profile and exhibits in man hypnotic activity similar to that of some BZD such as nitrazepam. The interaction of ZPC with rat brain receptors and esp. with the BZD receptors was studied. ZPC possesses in 3 rat brain regions a high affinity for BZD receptors; its Ki values measured against flunitrazepam are 24 nM in the cerebral cortex, 31 nM in the cerebellum, and 36 nM in the hippocampus. No other brain **receptors**, such as those for **GABA**, dopamine, serotonin, and noradrenaline, are reached by ZPC. Moreover, ZPC seems to bind only to brain BZD receptors and, contrarily to some BZD such as flunitrazepam, it does not reach the peripheral renal BZD-binding sites. The high affinity of ZPC was confirmed by equil.-binding studies (KD = 13 nM in rat hippocampus). A study of the modulating effect of GABA and barbiturates on ZPC binding revealed some differences between ZPC and BZD. It could, therefore, be postulated that ZPC might bind to rat brain sites which do not correspond exactly with BZD sites.

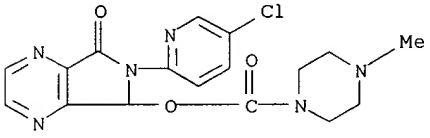
IT **43200-80-2**
RL: PROC (Process)
(binding of, to brain receptors)

RN 43200-80-2 HCAPLUS
CN 1-Piperazinecarboxylic acid, 4-methyl-, 6-(5-chloro-2-pyridinyl)-6,7-dihydro-7-oxo-5H-pyrrolo[3,4-b]pyrazin-5-yl ester (9CI) (CA INDEX NAME)

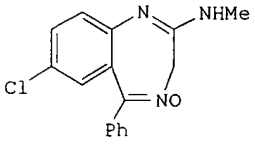


L34 ANSWER 52 OF 55 HCAPLUS COPYRIGHT 2000 ACS
AN 1983:498791 HCAPLUS
DN 99:98791

TI Differential modulation of [35S]TBPS binding by the occupancy of benzodiazepine receptors with its ligands
AU Supavilai, Porntip; Karobath, Manfred
CS Preclin. Res., Sandoz Ltd., Basel, CH-4002, Switz.
SO Eur. J. Pharmacol. (1983), 91(1), 145-6
CODEN: EJPHAZ; ISSN: 0014-2999
DT Journal
LA English
AB Binding of 35S-labeled t-butylbicyclophosphorothionate (I) [70636-86-1] to rat cerebral cortex was enhanced by benzodiazepine receptor agonists, inhibited by inverse benzodiazepine receptor agonists, and not markedly affected by benzodiazepine receptor antagonists. Apparently, I binding sites are constituents of the **GABA**-benzodiazepine **receptor** complex.
IT **43200-80-2**
RL: BIOL (Biological study)
(brain butylbicyclophosphorothionate binding response to, benzodiazepine receptors in relation to)
RN 43200-80-2 HCAPLUS
CN 1-Piperazinecarboxylic acid, 4-methyl-, 6-(5-chloro-2-pyridinyl)-6,7-dihydro-7-oxo-5H-pyrrolo[3,4-b]pyrazin-5-yl ester (9CI) (CA INDEX NAME)



L34 ANSWER 53 OF 55 HCAPLUS COPYRIGHT 2000 ACS
AN 1983:464167 HCAPLUS
DN 99:64167
TI Enhancement of GABA binding by benzodiazepines and related anxiolytics
AU Skerritt, John H.; Johnston, Graham A. R.
CS Dep. Pharmacol., Univ. Sydney, Sydney, 2006, Australia
SO Eur. J. Pharmacol. (1983), 89(3-4), 193-8
CODEN: EJPHAZ; ISSN: 0014-2999
DT Journal
LA English
GI

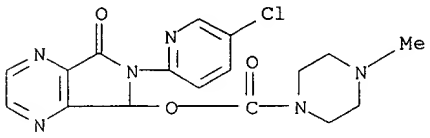


I

AB Several benzodiazepines (chlordiazepoxide (I) [58-25-3], clonazepam [1622-61-3], diazepam [439-14-5], midazolam maleate [59467-94-6], nitrazepam [146-22-5], and oxazepam [604-75-1]) produced a concn.-dependent enhancement of low-affinity GABA [56-12-2] binding to fresh, washed brain membranes in 50 mM Tris-citrate buffer at concns. comparable to those displacing [3H]diazepam binding in vitro. The nonbenzodiazepine anxiolytics CL218872 [66548-69-4] and zopiclone [**43200-80-2**] also enhanced GABA binding, while the centrally inactive benzodiazepine Ro5-4864 [14439-61-3] failed to alter GABA binding. The benzodiazepine antagonist Ro15-1788 [78755-81-4] did not alter GABA binding but potently antagonized stimulation of GABA binding by 100 nM diazepam. These pharmacol. characteristics suggest that an enhancement of the binding of **GABA** to low-affinity

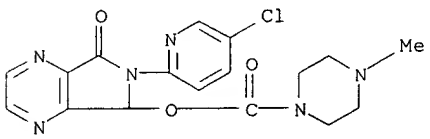
receptor sites may give rise to many of the in vivo actions of the benzodiazepines.

IT **43200-80-2**
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(GABA binding by brain response to)
RN 43200-80-2 HCAPLUS
CN 1-Piperazinecarboxylic acid, 4-methyl-, 6-(5-chloro-2-pyridinyl)-6,7-dihydro-7-oxo-5H-pyrrolo[3,4-b]pyrazin-5-yl ester (9CI) (CA INDEX NAME)



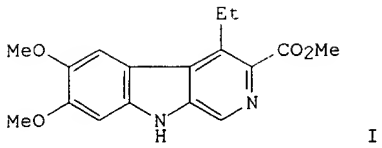
L34 ANSWER 54 OF 55 HCAPLUS COPYRIGHT 2000 ACS
AN 1982:609214 HCAPLUS
DN 97:209214
TI Contrasting regulation by GABA of the displacement of benzodiazepine antagonist binding by benzodiazepine agonists and purines
AU Skerritt, John H.; Davies, Les P.; Chow, Shirley Chen; Johnston, Graham A. R.
CS Dep. Pharmacol., Univ. Sydney, Sydney, 2006, Australia
SO Neurosci. Lett. (1982), 32(2), 169-74
CODEN: NELED5; ISSN: 0304-3940
DT Journal
LA English
AB GABA [56-12-2] Increases the potency of the benzodiazepines chlordiazepoxide [58-25-3], clonazepam [1622-61-3], diazepam [439-14-5], nitrazepam [146-22-5], and oxazepam [604-75-1], and the triazolopyridazine CL 218872 [66548-69-4], in displacing specific binding of the benzodiazepine antagonist [3H]Ro 15-1788. In contrast, the potencies of the purines 1-methyl [70639-65-5] and 1-ethylisoguanosine [73691-64-2] for benzodiazepine antagonist binding sites were decreased by GABA, whereas the potencies of inosine [58-63-9], hypoxanthine [68-94-0], 6-dimethylaminopurine [938-55-6], and the non-benzodiazepine anxiolytic, zopiclone **[43200-80-2]**, were unaltered by GABA. Apparently, purines and classical benzodiazepine agonists may bind to different conformations or populations of receptors.

IT **43200-80-2**
RL: BIOL (Biological study)
(benzodiazepine **receptor** affinity for, **GABA** in relation to)
RN 43200-80-2 HCAPLUS
CN 1-Piperazinecarboxylic acid, 4-methyl-, 6-(5-chloro-2-pyridinyl)-6,7-dihydro-7-oxo-5H-pyrrolo[3,4-b]pyrazin-5-yl ester (9CI) (CA INDEX NAME)



L34 ANSWER 55 OF 55 HCAPLUS COPYRIGHT 2000 ACS
AN 1982:465921 HCAPLUS
DN 97:65921
TI Interaction of convulsive ligands with benzodiazepine receptors
AU Braestrup, C.; Schmiechen, R.; Neef, G.; Nielsen, M.; Petersen, E. N.
CS Res. Lab., A/S Ferrosan, Soeborg, Den.
SO Science (Washington, D. C., 1883-) (1982), 216(4551), 1241-3
CODEN: SCIEAS; ISSN: 0036-8075

DT Journal
LA English
GI

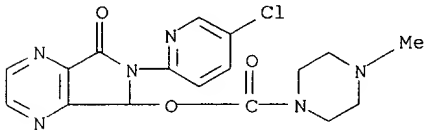


I

AB The .**gamma**.-**aminobutyric acid** (**GABA**) [56-12-2]-benzodiazepine [12794-10-4] **receptor** complex, which is composed of distinct proteins embedded in the neuronal plasma membrane, is important for several effects of benzodiazepines, including protection afforded against convulsions. Me 6,7-dimethoxy-4-ethyl-.beta.-carboline-3-carboxylate (I) [82499-00-1], an Et .beta.-carboline-3-carboxylate analog, has high affinity for brain benzodiazepine receptors and is a potent convulsant. Also in contrast to benzodiazepines, I and benzodiazepine receptor ligands similar to I favor benzodiazepine **receptors** in the non-**GABA**-stimulated conformation, which may explain their convulsive properties.

IT **43200-80-2**
RL: BIOL (Biological study)
(binding of, by benzodiazepine **receptors, GABA** effect on)

RN 43200-80-2 HCAPLUS
CN 1-Piperazinecarboxylic acid, 4-methyl-, 6-(5-chloro-2-pyridinyl)-6,7-dihydro-7-oxo-5H-pyrrolo[3,4-b]pyrazin-5-yl ester (9CI) (CA INDEX NAME)



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=> d ti 1-2 136

L36 ANSWER 1 OF 2 HCAPLUS COPYRIGHT 2000 ACS
TI Characterization of novel ligands for wild-type and natural mutant diazepam-insensitive benzodiazepine receptors

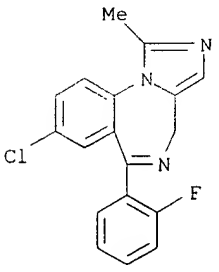
← this cite is ↘ L34 10/55

L36 ANSWER 2 OF 2 HCAPLUS COPYRIGHT 2000 ACS
TI RP 59037 and RP 60503: Anxiolytic cyclopyrrolone derivatives with low sedative potential. Interaction with the .gamma.-aminobutyric acidA/benzodiazepine receptor complex and behavioral effects in the rodent

L34 14/35

=> d bib abs hitstr l132 1-45

L132 ANSWER 1 OF 45 HCAPLUS COPYRIGHT 2000 ACS
AN 1999:319705 HCAPLUS
DN 131:139350
TI The effects of midazolam on pure tone audiometry, speech audiometry, and audiological reaction times in human volunteers
AU Kelly, Dermot J.; Walsh, Fergus; Norman, Gary S.; Cunningham, Anthony J.
CS Department of Anaesthesia, St. Vincent's Hospital, Dublin, Ire.
SO Anesth. Analg. (Baltimore) (1999), 88(5), 1064-1068
CODEN: AACRAT; ISSN: 0003-2999
PB Lippincott Williams & Wilkins
DT Journal
LA English
AB Auditory evoked potentials are effected by benzodiazepines, as is cortical processing of auditory stimuli. The effect of benzodiazepines on auditory sensitivity has not, however, been studied. We designed the present study to investigate the effect of sedative doses of midazolam on pure tone and speech audiometry and on audiol. reaction times in healthy volunteers. Thirty volunteers underwent baseline audiol. assessment for pure tones and speech and had their audiol. reaction times measured at 10 and 50 dB above their threshold hearing level at a frequency of 1 kHz. Subjects were then randomly assigned to one of two groups. Group A (n = 15) received midazolam (0.04 mg/kg) IV, and Group B (n = 15) received a similar vol. of placebo IV. The audiol. tests were repeated 5 min later, and performance was compared with baseline data. Scheffe post hoc tests were used to assess the significance of changes in each group. There was no pre- to posttest change in audiol. performance in either the placebo group (P = 0.194) or the midazolam group (P = 0.957). Speech audiometry performance was likewise unaffected by midazolam (P = 0.154). Reaction time at the 10-dB and 50-dB sensation levels were both significantly prolonged after midazolam administration (P = 0.023 and P = 0.012, resp.). In this study, we demonstrate that sedation with midazolam (0.04 mg/kg) does not alter pure tone or speech audiometric thresholds, but it does significantly delay the reaction time to auditory stimuli. Medical practitioners should advise midazolam-sedated patients of their impaired reaction to auditory warning signals (e.g., traffic and car horns) as part of the day-ward discharge recommendations.
IT **59467-70-8**, Midazolam
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(effects of midazolam on pure tone audiometry, **speech** audiometry, and audiol. reaction times in human volunteers)
RN 59467-70-8 HCAPLUS
CN 4H-Imidazo[1,5-a][1,4]benzodiazepine, 8-chloro-6-(2-fluorophenyl)-1-methyl- (9CI) (CA INDEX NAME)



RE.CNT 20
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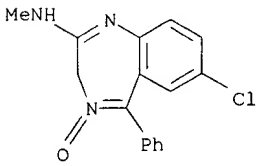
(1) Allonen, H; Clin Pharmacol Ther 1981, V30, P653 HCAPLUS
(3) Bill, K; J R Soc Med 1991, V84, P277 MEDLINE
(6) De Roode, A; Anaesthesia 1995, V50, P191 MEDLINE
(11) Lader, M; Auditory evoked potentials in man: psychopharmacology correlates of evoked potential 1977, P142 HCAPLUS
(15) Reinsel, R; Anesth Analg 1991, V73, P612 HCAPLUS

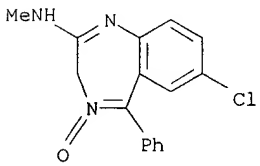
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L132 ANSWER 2 OF 45 HCAPLUS COPYRIGHT 2000 ACS
AN 1998:638343 HCAPLUS
DN 130:10569
TI Dissociation of consummatory and vocal components of feeding in squirrel monkeys treated with benzodiazepines and alcohol
AU Weerts, Elise M.; Macey, Darrel J.; Miczek, Klaus A.
CS Department of Psychology, Tufts University, Medford, MA, 02155, USA
SO Psychopharmacology (Berlin) (1998), 139(1/2), 117-127
CODEN: PSCHDL; ISSN: 0033-3158
PB Springer-Verlag
DT Journal
LA English
AB The primary aim of the current expts. was to develop methods that engender vocalizations assocd. with pos. social situations comprising affiliative behavior and feeding that could be quantified under controlled lab. conditions and were sensitive to anxiolytic drugs. Classical conditioning procedures were used to elicit vocalizations during presentation of stimulus lights (i.e., CS condition) previously paired with either preferred foods (e.g., grapes, peanuts, bananas) or std. foods (e.g., monkey chow) as well as during presentation of both food types (i.e., UCS condition). When compared to the period before stimulus light presentation (i.e., Pre-CS condition), the rate, duration and no. of elemental units of food-related "twitter" vocalizations were increased during the CS conditions regardless of food type. Monkeys spent significantly more time oriented toward the food box during the light stimulus that preceded preferred food than for the light stimulus that preceded std. food. However, twitter vocalizations were higher for std. food regardless of the stimulus conditions (i.e., Pre-CS, CS and UCS). Administration of the benzodiazepine full agonist chlordiazepoxide (CDP, 1-10 mg/kg), the partial agonist bretazenil (BRZ, 1-10 mg/kg), the antagonist flumazenil (FLZ, 1-10 mg/kg) and Et alc. (EtOH, 0.1-1.0 g/kg) differentially altered vocalizations. Although CDP and BRZ increased feeding of std. food, twitters were reduced across stimulus conditions. CDP and BRZ did not alter other social contact calls (i.e., "peeps"). FLZ also reduced twitters without altering peeps, but did not increase feeding. In contrast, EtOH did not increase feeding or peeps, but did increase food-related twitters. These results indicate that there is a dissocn. between food-related behaviors, such as food consumption and orientation towards the food source, and vocal behaviors assocd. with group communication during feeding.
IT **58-25-3**, Chlordiazepoxide
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(dissocn. of consummatory and **vocal** components of feeding in squirrel monkeys treated with benzodiazepines and alc.)
RN 58-25-3 HCAPLUS
CN 3H-1,4-Benzodiazepin-2-amine, 7-chloro-N-methyl-5-phenyl-, 4-oxide (9CI) (CA INDEX NAME)



RE.CNT 60
RE
(2) Barrett, J; J Pharmacol Exp Ther 1976, V196, P605 HCAPLUS
(5) Berridge, K; Pharmacol Biochem Behav 1986, V24, P217 HCAPLUS
(9) Britton, D; Pharmacol Biochem and Behav 1981, V15, P577 HCAPLUS
(12) Cooper, S; Brain Res Bull 1987, V19, P347 HCAPLUS
(13) Cooper, S; Eur J Pharmacol 1985, V112, P39 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L132 ANSWER 3 OF 45 HCAPLUS COPYRIGHT 2000 ACS
AN 1996:678743 HCAPLUS
DN 126:2942
TI Primate vocalizations during social separation and aggression. Effects of alcohol and benzodiazepines
AU Weerts, Elise M.; Miczek, Klaus A.
CS Dep. Psychology, Tufts Univ., Medford, MA, 02155, USA
SO Psychopharmacology (Berlin) (1996), 127(3), 255-264
CODEN: PSCHDL; ISSN: 0033-3158
PB Springer
DT Journal
LA English
AB The pharmacol. alteration of peeps and other vocalizations of squirrel monkeys emitted during different social contexts was studied. Vocalizations were characterized during (1) social sepn. in juveniles, and (2) "resident-intruder" aggressive confrontations between dominant monkeys from different social groups. The effects of EtOH and the benzodiazepine chlordiazepoxide (CDP) on vocalizations during social sepn. and during aggression were examd. Isolated juveniles emitted only the isolation peep. Resident monkeys primarily emitted peeps, but also emitted cackles, chucks, noisy calls and pulsed calls. Aggressive peeps were similar in structure and frequency (kHz) to isolation peeps, but were shorter in duration. At the same doses, both CDP (0.3-3 mg/kg) and EtOH (0.1-1.0 g/kg) reduced explosive motor behavior and isolation peeps in juvenile monkeys during social sepn. and increased threat displays and aggression peeps in resident monkeys during confrontations with an intruder monkey from a different social group. Similarly structured vocalizations that were emitted during social sepn. and aggression were very sensitive to EtOH and CDP, but the social context detd. the direction and magnitude of effects.
IT **58-25-3D**, Chlordiazepoxide, Benzodiazepine
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(alc. and benzodiazepines effect on **vocalizations** during social sepn. and aggression)
RN 58-25-3 HCAPLUS
CN 3H-1,4-Benzodiazepin-2-amine, 7-chloro-N-methyl-5-phenyl-, 4-oxide (9CI) (CA INDEX NAME)



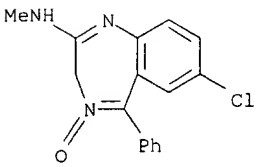
L132 ANSWER 4 OF 45 HCAPLUS COPYRIGHT 2000 ACS
AN 1994:236417 HCAPLUS
DN 120:236417
TI Ultrasound vocalization is not related to corticosterone response in isolated rat pups
AU Klint, Thorsten; Andersson, Gunnar
CS Dep. CNS Res., Kabi Pharmacia Therapeutics, Malmoe, S-201 80, Swed.
SO Pharmacol., Biochem. Behav. (1994), 47(4), 947-50
CODEN: PBBHAU; ISSN: 0091-3057
DT Journal
LA English
AB Isolated from their mother, rat pups respond with changes in ultrasound vocalization (USV), a paradigm that can be used as a test for a large range of anxiolytics. Because the relation between corticosterone (CORT) and putative stress responses like USV is not clear, the authors examd. the effects of the benzodiazepine drugs chlordiazepoxide and diazepam vs. the nonbenzodiazepine drugs buspirone and 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT) on USV and plasma CORT concns. All drugs caused a dose-related decrease in USV, but only buspirone and 8-OH-DPAT induced a dose-related increase in CORT. The authors suggest that the seemingly paradoxical effects of buspirone and 8-OH-DPAT, i.e., the

decrease in USV and the concomitant increase in plasma CORT, are due to the fact that these two drugs act as full agonists at both pre- and postsynaptic 5-HT1A receptors. The authors' results indicate that, when measured as an increase in the activity of the pituitary adrenocortical axis, the stress response can be interpreted in markedly different ways, depending on whether the increased activity is elicited by an environmental stressor or by pharmacol. manipulation.

IT **58-25-3**, Chlordiazepoxide
RL: BIOL (Biological study)
(corticosterone release response to, ultrasound **vocalization** inhibition in relation to)

RN 58-25-3 HCAPLUS

CN 3H-1,4-Benzodiazepin-2-amine, 7-chloro-N-methyl-5-phenyl-, 4-oxide (9CI) (CA INDEX NAME)



L132 ANSWER 5 OF 45 HCAPLUS COPYRIGHT 2000 ACS

AN 1994:69423 HCAPLUS

DN 120:69423

TI Shock-induced ultrasonic vocalization in young adult rats: A model for testing putative anti-anxiety drugs

AU De Vry, Jean; Benz, Ulrich; Schreiber, Rudy; Traber, Jorg

CS Dep. Psychopharmacol., Inst. Neurobiol., Cologne, D-51063, Germany

SO Eur. J. Pharmacol. (1993), 249(3), 331-9
CODEN: EJPHAZ; ISSN: 0014-2999

DT Journal

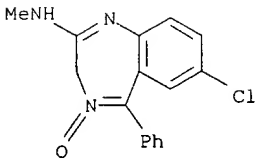
LA English

AB A putative animal model of anxiety based on shock-induced ultrasonic vocalization was pharmacol. validated in young adult rats. Suppression of shock-induced ultrasonic vocalization was obtained with diazepam, chlordiazepoxide, meprobamate and pentobarbital; the serotonin (5-HT)1A receptor agonists 8-OH-DPAT [8-hydroxy-2-(di-n-propylamino)tetralin], buspirone, ipsapirone, gepirone and tandospirone; the nonselective 5-HT receptor agonists TFMPP [1-(3-trifluoromethylphenyl)piperazine], mCPP [1-(3-chlorophenyl)piperazine] and DOI (1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane); the NMDA antagonists PCP (phencyclidine) and MK-801; the .alpha.2-adrenoceptor antagonists idazoxane, yohimbine and 1-PP (1-pyrimidinylpiperazine); and the atypical neuroleptic clozapine. The .alpha.2-adrenoceptor agonist clonidine, the 5-HT2/5-HT1C antagonist ritanserin, the 5-HT3antagonists ondansetron and ICS-205,930, and the 5-HT reuptake inhibitor fluoxetine did not, or only partially, reduce ultrasonic vocalization. Tricyclic and tetracyclic, as well as some atypical antidepressants and a monoamineoxidase (MAO) inhibitor, showed no ultrasonic vocalization reducing effects, or reduced ultrasonic vocalization only at high doses. An opiate, an antimuscarinic, (pro)convulsants and typical neuroleptics did not reduce ultrasonic vocalization. The present findings suggest that the ultrasonic vocalization model specifically measures anxiolytic effects. Because ultrasonic vocalization responding develops within five days, remains stable for at least three months and gives highly reproducible results, the test appears suitable for rapid and repeated testing of new anxiolytics in the same animals.

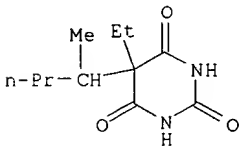
IT **58-25-3**, Chlordiazepoxide **76-74-4**, Pentobarbital
RL: BIOL (Biological study)
(antianxiety activity of, shock-induced ultrasonic **vocalization** in testing)

RN 58-25-3 HCAPLUS

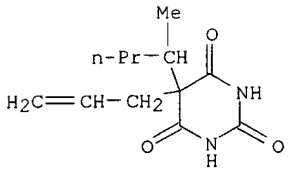
CN 3H-1,4-Benzodiazepin-2-amine, 7-chloro-N-methyl-5-phenyl-, 4-oxide (9CI) (CA INDEX NAME)



RN 76-74-4 HCAPLUS
CN 2,4,6(1H,3H,5H)-Pyrimidinetrione, 5-ethyl-5-(1-methylbutyl)- (9CI) (CA INDEX NAME)



L132 ANSWER 6 OF 45 HCAPLUS COPYRIGHT 2000 ACS
AN 1990:48698 HCAPLUS
DN 112:48698
TI Monolog speech: effects of d-amphetamine, secobarbital and diazepam
AU Higgins, Stephen T.; Stitzer, Maxine L.
CS Dep. Psychiatry, Univ. Vermont, Burlington, VT, 05401, USA
SO Pharmacol., Biochem. Behav. (1989), 34(3), 609-18
CODEN: PBBHAU; ISSN: 0091-3057
DT Journal
LA English
AB The acute effects of secobarbital (0, 50, 150, 250 mg), d-amphetamine (0, 25 mg) (Expt. 1), and diazepam (0, 10, 20, 40 mg) (Expt. 2) were investigated in healthy, adult volunteers. Secobarbital and d-amphetamine both increased the total amt. of monolog speech, while diazepam generally had no effect or decreased talking. Expt. 3 was conducted to further compare the effects of secobarbital (0, 50, 150, 250 mg) and diazepam (0, 5, 15, 25 mg) using a within-subject, crossover design. Secobarbital increased talking in 3 of the 4 subjects studied, while diazepam, again, had no effect or decreased talking. In contrast to the differences noted with talking, secobarbital and diazepam both decreased response rates in a nonverbal performance task (i.e., circular-lights procedure); they also produced many similar effects on various subject-rated measures of drug effect. Thus, the differences in the effects of these 2 compds. on talking are not the result of a general difference in their overall profile of behavioral effects. In summary, the results obtained with secobarbital and d-amphetamine further demonstrate that an explicitly social context is not a necessary condition to observe drug-produced increases in speech quantity. The failure of diazepam to reliably increase talking in the present study illustrates the existence of some pharmacol. specificity in the effect of drugs on human speech, and suggests another way in which the behavioral effects of the barbiturates and benzodiazepines may differ.
IT **76-73-3**, Secobarbital
RL: BIOL (Biological study)
(monolog **speech** response to, in human)
RN 76-73-3 HCAPLUS
CN 2,4,6(1H,3H,5H)-Pyrimidinetrione, 5-(1-methylbutyl)-5-(2-propenyl)- (9CI) (CA INDEX NAME)



L132 ANSWER 7 OF 45 HCAPLUS COPYRIGHT 2000 ACS
AN 1987:189256 HCAPLUS
DN 106:189256
TI The reproductive status of four Jersey herds as evaluated by levels of progesterone in milk
AU Robert, O.; Taylor, R. T.
CS Esc. Med. Vet., UNA, Heredia, Costa Rica
SO Turrialba (1986), 36(2), 179-86
CODEN: TURRAB; ISSN: 0041-4360
DT Journal
LA Spanish
AB Progesterone (I) [**57-83-0**] in milk was detd. by RIA to evaluate its usefulness in characterizing the estrus cycle of Jersey cows, and hence in maximizing reproductive success. Daily levels of I were detd. for 23 days in defatted milk of cyclic cows or cows artificially-inseminated at day 1 of the survey. In uninseminated cows, I was >1 ng/mL during days 3-18 of the estrus cycle; I levels were low at the beginning and end of the cycle. Inseminated cows showed similar patterns of I until day 17; thereafter I continued to increase. I monitoring permitted **unequivocal** identification for all animals returning to estrus.

L132 ANSWER 8 OF 45 HCAPLUS COPYRIGHT 2000 ACS
AN 1987:188907 HCAPLUS
DN 106:188907
TI The histopathology and biochemistry of phenobarbitone-induced liver nodules in C3H mice
AU Gangolli, S. D.; Lake, B. G.; Evans, J. G.
CS Br. Ind. Biol. Res. Assoc., Carshalton, SM5 4DS, UK
SO Arch. Toxicol., Suppl. (1987), 10(Mouse Liver Tumors), 95-107
CODEN: ATSUDG; ISSN: 0171-9750
DT Journal
LA English
AB The sequential development of hepatic nodules induced by phenobarbitone (PB) [**50-06-6**] was studied in the C3H/He strain of mouse, a strain prone to the development of spontaneous liver tumors. PB was administered in the diet to young male animals at a dose level of 85 mg/kg/day for .ltoreq.91 wk. Control and PB-treated mice developed hepatic nodules within 60 wk. In control animals, the nodules consisted of small basophilic cells, and by 80 wk a small proportion of the animals had developed **unequivocal** hepatocellular carcinoma. The basophilic nodules were similar in many respects to those induced by N-nitrosodiethylamine. In PB-treated mice, the incidence of basophilic nodules was similar to that in controls. These animals also developed hepatic nodules formed of large eosinophilic cells which were readily dissectable from the surrounding host tissue by 60 wk. Biochem. investigations into the large eosinophilic nodules from PB-treated mice showed that both phase I and phase II types of xenobiotic-metabolizing enzyme activities were induced to levels either similar to, or greater than in the surrounding host tissue. In contrast, enzyme activities in basophilic nodules from untreated mice killed at 91 wk, were generally similar to or lower than in the surrounding host tissue. The presence of eosinophilic nodules did not lead to an increase in the incidence of hepatocellular carcinoma in the PB-treated C3H/He mice. Concurrent expts. conducted in the C57BL/6 strain of mouse did not result in the development of liver nodules at 60 wk. Thus, the eosinophilic nodules induced by PB in C3H/He mice appear to be distinctly different from the basophilic liver nodules arising spontaneously or to basophilic nodules produced by the hepatocellular carcinogen N-nitrosodiethylamine.

L132 ANSWER 9 OF 45 HCAPLUS COPYRIGHT 2000 ACS
AN 1986:585529 HCAPLUS
DN 105:185529
TI Effects of administration of metabolic inducers and inhibitors on pulmonary toxicity and covalent binding by 1,1-dichloroethylene in CD-1 mice
AU Forkert, P. G.; Stringer, V.; Racz, W. J.
CS Dep. Anat., Queen's Univ., Kingston, ON, K7L 3N6, Can.
SO Exp. Mol. Pathol. (1986), 45(1), 44-58
CODEN: EXMPA6; ISSN: 0014-4800
DT Journal
LA English
AB The administration of 1,1-dichloroethylene (1,1-DCE) [75-35-4] (125 mg/kg, i.p.) to CD-1 mice caused bronchiolar necrosis, which was accompanied by substantial covalent binding of radiolabeled compd. and/or metabolite to lung. Lung injury and covalent binding were not modified by phenobarbital [**50-06-6**] pretreatment. However, methylcholanthrene [56-49-5] provided a protective influence but failed to alter covalent binding to lung macromols. Prior administration with the metabolic inhibitors, piperonyl butoxide [51-03-6] and SKF 525-A produced differential effects. While piperonyl butoxide exacerbated bronchiolar injury by 1,1-DCE, covalent binding remained unaltered. In contrast, SKF 525-A protected from lung damage and significantly decreased covalent binding. Hepatic necrosis was relatively mild, and was not obsd. in all animals treated with 1,1--DCE. Although the hepatic lesion was not modified by phenobarbital, liver injury was slightly diminished by 3-methylcholanthrene. The inducers, piperonyl butoxide and SKF 525-A, enhanced liver necrosis, with the latter eliciting more severe effects than the former agent. Covalent binding to liver tissues was not significantly changed by pretreatment with inducers or inhibitors. Thus, lack of an **unequivocal** correlation of cellular injury with covalent binding suggests that metab. may be involved in the pneumotoxicity by 1,1-DCE.

L132 ANSWER 10 OF 45 HCAPLUS COPYRIGHT 2000 ACS
AN 1986:454484 HCAPLUS
DN 105:54484
TI Behavioral pharmacological effects of zopiclone in rats and rhesus monkeys
AU Ando, Kiyoshi; Takada, Kohji; Yanagita, Tomoji
CS Dep. Psychopharmacol., Cent. Inst. Exp. Anim., Kawasaki, 213, Japan
SO Jitchuken Zenrinsho Kenkyuho (1985), 11(1), 1-20
CODEN: JZKEDZ; ISSN: 0385-8502
DT Journal
LA Japanese
AB In rats under the differential reinforcement of low rate schedule, zopiclone (I) [**43200-80-2**] (8 mg/kg or more orally caused disruption of timing behavior similar to that with diazepam (II) as indicated by an increase in the variability of interresponse times (IRTs) with little change in the no. of responses. Under the conflict procedure using rhesus monkeys, I had an attenuating effect on conditioned suppression similar to that obsd. with II at 1 mg/kg or more orally. In a drug discrimination test using 2 rhesus monkeys, the discriminative effect of pentobarbital (III) was generalized to II, chlordiazepoxide, and EtOH in both monkeys, but to I in only 1 monkey. Thus, the generalization from III to I was **equivocal**. In conclusion, the behavioral pharmacol. effects of I were comparable with II quant. and qual. in 2 types of schedule-controlled behaviors using rats and rhesus monkeys although the discriminative effects of I appeared to be somewhat different from those of II.

L132 ANSWER 11 OF 45 HCAPLUS COPYRIGHT 2000 ACS
AN 1986:200156 HCAPLUS
DN 104:200156
TI Effect of single and repeated treatment of chlordiazepoxide and sodium valproate on water intake in the rat and their influence on the antidipsogenic action of naloxone
AU Cannizzaro, G.; Brucato, A. Flugy; Provenzano, P. M.
CS Inst. Pharmacol., Univ. Palermo, Italy
SO Arzneim.-Forsch. (1986), 36(4), 718-21
CODEN: ARZNAD; ISSN: 0004-4172

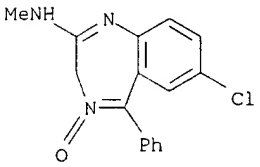
DT Journal
LA English
AB The action of single and repeated treatment with chlordiazepoxide (CDP) [**58-25-3**] (5-10 mg/kg, i.p.) and valproate (VPA) [99-66-1] (100-200 mg/kg, i.p.) on water intake of rats adapted to a daily 23-h water deprivation schedule was investigated. The influence exerted by single or repeated treatment with the 2 drugs on the antidipsogenic effect of naloxone (Nx) [465-65-6] (1 mg/kg s.c.) was also studied. With single treatment with CDP, the dipsogenic effect was lower and not further modified by increasing the dose and by the time-course of the session; with repeated treatment, the dipsogenic effect was greater and further enhanced by increasing the dose and by the time-course of the session. Single or repeated treatment with VPA did not significantly affect the water intake. Single treatment with CDP enhanced the antidipsogenic effect of Nx, whereas CDP, after repeated treatment, reversed the antidipsogenic effect of Nx. With the VPA-Nx assocn., the response was **univocal** (antidopsogenic effect) independent of the exptl. conditions. The results are briefly discussed in relation to the effect of the drugs on GABAergic neurotransmission.

L132 ANSWER 12 OF 45 HCAPLUS COPYRIGHT 2000 ACS
AN 1986:14988 HCAPLUS
DN 104:14988
TI Sex differences in the induction of physical dependence on pentobarbital in the rat
AU Suzuki, Tsutomu; Koike, Yoko; Yoshii, Toshio; Yanaura, Saizo
CS Sch. Pharm., Hoshi Univ., Tokyo, 142, Japan
SO Jpn. J. Pharmacol. (1985), 39(4), 453-9
CODEN: JJPAAZ; ISSN: 0021-5198
DT Journal
LA English
AB Sex differences in phys. dependence on pentobarbital [**76-74-4**] in the rat were studied by the drug-admixed food (DAF) method. With male rats, the concn. of pentobarbital in the food was gradually increased from 2 to 30 mg/g over a period of 50 days. The final level of drug intake was approx. 1.7 g/kg/day. At pentobarbital concns. of 20 and 22 mg/g of food, sedation and mild muscle relaxation were obsd. At the highest drug concn., 30 mg/g of food, marked muscle relaxation was noted. With female rats, the concn. of pentobarbital in the food was gradually increased from 1 to 16 mg/g over a period of 47 days. The final level of intake was approx. 1.0 mg/kg/day. At drug concns. of 12 and 14 mg/g, sedation and mild muscle relaxation appeared. At 16 mg/g, female rats showed marked muscle relaxation similar to that of the male rats. To produce severe loss of muscle tone, the male rats required twice as much pentobarbital as the female rats. After substitution of normal food for the pentobarbital-admixed food, various signs of pentobarbital withdrawal occurred in both sexes. These signs included **vocalization**, irritability, muscle rigidity, tremors and convulsions. Onset of withdrawal was more rapid in the females, and the max. wt. loss was greater, 8.0% compared to 3.8% in the males. Phys. dependence on pentobarbital was easily developed in both sexes by the DAF method. There was a marked sex difference in withdrawal which we attribute to sex differences in drug metabolizing enzyme activity.

L132 ANSWER 13 OF 45 HCAPLUS COPYRIGHT 2000 ACS
AN 1985:589084 HCAPLUS
DN 103:189084
TI Distress vocalization in rat pups. A simple screening method for anxiolytic drugs
AU Gardner, C. R.
CS Roussel Lab. Ltd., Covingham/Swindon/Wiltshire, SN3 5BZ, UK
SO J. Pharmacol. Methods (1985), 14(3), 181-7
CODEN: JPMED9; ISSN: 0160-5402
DT Journal
LA English
AB A method is described for reproducible measurement of ultrasonic **vocalization** induced by tail-holding stress in rat pups. The anxiolytic benzodiazepines, chlordiazepoxide [**58-25-3**], diazepam [439-14-5], and CL 218872 [66548-69-4], reduced the ultrasounds at doses inducing little central nervous system depressant activity.

Gross behavioral disruption such as sedation (muscimol [2763-96-4], prazosin [19216-56-9], and chlorpromazine [50-53-3]), tremors (yohimbine [146-48-5]), myoclonus (MK 212 [64022-27-1]), and immobility (morphine [57-27-2]) resulted in redn. of ultrasounds. Non-behaviorally active doses of these compd. or any doses tested of mephenesin [59-47-2], amphetamine [300-62-9], amitriptyline [50-48-6], haloperidol [52-86-8], and naloxone [465-65-6] did not affect the ultrasounds. Metergoline [17692-51-2] inhibited ultrasounds at doses producing little change in overt behavior. This method is proposed as a convenient model of anxiety which may also be influenced by central 5-hydroxytryptamine transmission.

IT **58-25-3**
RL: BIOL (Biological study)
(ultrasound **vocalization** response to, in anxiolytic drug screening)
RN 58-25-3 HCAPLUS
CN 3H-1,4-Benzodiazepin-2-amine, 7-chloro-N-methyl-5-phenyl-, 4-oxide (9CI) (CA INDEX NAME)



L132 ANSWER 14 OF 45 HCAPLUS COPYRIGHT 2000 ACS
AN 1985:417003 HCAPLUS
DN 103:17003
TI Relationship between progesterone receptor binding and progestin biological activity
AU Spilman, C. H.; Wilks, J. W.; Campbell, J. A.
CS Upjohn Co., Kalamazoo, MI, 49001, USA
SO J. Steroid Biochem. (1985), 22(3), 289-92
CODEN: JSTBBK; ISSN: 0022-4731
DT Journal
LA English
AB The binding affinities of a series of steroidal compds. for the hamster uterine progesterone **[57-83-0]** receptor were detd. by using 2 sets of incubation conditions. These competitive binding conditions were designed to deduce the relative rates of ligand dissocn. from the progesterone receptor. The progestin activity of these compds. was also detd. in a bioassay employing the measurement of diamine oxidase in the traumatized hamster uterus. Steroids could be classified into 2 categories based on either an increase or decrease in relative binding affinity (RBA) with increasing time of competitive incubation. The mean progestin biopotency for the compds. having an increase in RBA was 120 (progesterone = 100), whereas the biopotency for compds. having a decrease in RBA was only 44. Linear regression analyses revealed significant correlations between the RBAs and progestin biopotencies. Compds. showing a decrease in RBA with increasing time of incubation did not have antiprogestin activity. Kinetic studies of this type should be useful for selecting compds. with potent agonistic activity, but cannot **unequivocally** predict antihormonal activity.

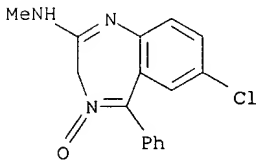
L132 ANSWER 15 OF 45 HCAPLUS COPYRIGHT 2000 ACS
AN 1985:125516 HCAPLUS
DN 102:125516
TI Inhibition of ultrasonic distress vocalizations in rat pups by chlordiazepoxide and diazepam
AU Gardner, C. R.
CS Roussel Lab., Covingham, UK
SO Drug Dev. Res. (1985), 5(2), 185-93
CODEN: DDREDK; ISSN: 0272-4391
DT Journal
LA English
AB Wistar rat pups emit ultrasonic distress cries when placed on a cold plate

or when held by the tail. Chlordiazepoxide [58-25-3] and diazepam [439-14-5] inhibited the sounds, and their activity was only assocd. with sedation and muscle relaxation at higher doses. The muscle relaxant mephenesin [59-47-2] had little effect. Prazosin [19216-56-9] induced sedation and hypothermia and inhibited sounds induced by tail holding more than those on the cold plate. Clonidine [4205-90-7] induced hypothermia and weak sedation and increased sound emission weakly for the tail holding response but markedly for responses on the plate. This sepn. of responses may result from potentiation of responses on the plate by drug-induced hypothermia. Although sedative effects result in decreased ultrasounds, the benzodiazepines continue to reduce sounds at doses showing little or no sedation. Thus, the benzodiazepines may reduce the sound via their anxiolytic action.

IT **58-25-3**
RL: BIOL (Biological study)
(stress-induced **vocalization** response to)

RN 58-25-3 HCAPLUS

CN 3H-1,4-Benzodiazepin-2-amine, 7-chloro-N-methyl-5-phenyl-, 4-oxide (9CI) (CA INDEX NAME)



L132 ANSWER 16 OF 45 HCAPLUS COPYRIGHT 2000 ACS

AN 1985:41326 HCAPLUS

DN 102:41326

TI Modifying potential of thirty-one chemicals on the short-term development of .gamma.-glutamyl transpeptidase-positive foci in diethylnitrosamine-initiated rat liver

AU Tsuda, Hiroyuki; Hasegawa, Ryohei; Imaida, Katsumi; Masui, Tsuneo; Moore, Malcolm A.; Ito, Nobuyuki

CS Med. Sch., Nagoya City Univ., Nagoya, 467, Japan

SO Gann (1984), 75(10), 876-83
CODEN: GANNA2; ISSN: 0016-450X

DT Journal

LA English

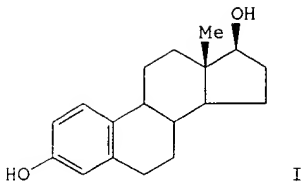
AB The modifying potential of 31 different compds. on the development of .gamma.-glutamyl transpeptidase [9046-27-9]-pos. (.gamma.-GT+) liver cell lesions was compared in an in vivo short-term assay system. Rats were initially given a single dose (200 mg/kg) of diethylnitrosamine [55-18-5] i.p. and 2 wk later were treated with test compds. for 6 wk and then sacrificed, all rats being subjected to partial hepatectomy at week 3. Modifying potential was scored by comparing the no. and area (mm2)/cm2 of induced .gamma.-GT+ foci with those of the corresponding control group given DEN alone. 2-Acetylaminofluorene [53-96-3], 3'-methyl-4-dimethylaminoazobenzene [55-80-1], dimethylnitrosamine [62-75-9], phenobarbital [**50-06-6**], barbital [57-44-3], dipyrone [68-89-3], and deoxycholic acid [83-44-3] caused a significant enhancement of both the no. and area of foci. 4-Acetylaminofluorene [28322-02-3], ethionine [13073-35-3], benzo[a]pyrene [50-32-8], disulfiram [97-77-8], and cholic acid [81-25-4] had a moderate enhancing effect, whereas slight, but not **unequivocal**, increases in .gamma.-GT+ foci were obsd. after captafol [2425-06-1], glutathione [70-18-8], Na ascorbate [134-03-2], and taurine [107-35-7] administration. In contrast, acetaminophen [103-90-2], ethoxyquin [91-53-2], butylated hydroxyanisole [25013-16-5], butylated hydroxytoluene [128-37-0], and ethyl alc. [64-17-5] showed clear inhibitory effects. Thus, the present short-term in vivo system has practical applications for the screening of modifying agents for liver tumorigenesis including hepatocarcinogens.

L132 ANSWER 17 OF 45 HCAPLUS COPYRIGHT 2000 ACS

AN 1984:416845 HCAPLUS
DN 101:16845
TI Interactions of cholinesterase inhibitors and corticosteroids with the hypnotic effect of benzodiazepines in mice
AU Leeuwin, R. S.
CS Pharmacol. Lab., Univ. Amsterdam, Amsterdam, Neth.
SO Arch. Int. Pharmacodyn. Ther. (1984), 269(1), 34-41
CODEN: AIPTAK; ISSN: 0003-9780
DT Journal
LA English
AB Interactions of cholinesterase [9001-08-5] inhibitors or dexamethasone [50-02-2] with the hypnotic effect of benzodiazepines appear to be strongly dependent on the dose of the cholinesterase inhibitor used and to a lesser extent on the dose of the hypnotic. The duration of the loss of righting reflex caused by the diazepam [439-14-5] or chlordiazepoxide [**58-25-3**], is markedly prolonged by 500 .mu.g/kg physostigmine [57-47-6], or 50 .mu.g/kg neostigmine [59-99-4], whereas neostigmine, 100 .mu.g/kg, antagonizes both diazepam and chlorodiazepoxide. Relatively higher doses of physostigmine have no significant effect on either diazepam or chlorodiazepoxide. Dexamethasone, in relatively low doses of 250 and 500 .mu.g/kg or 500 .mu.g/kg resp., significantly reverses the effect of diazepam and chlorodiazepoxide, while in relatively high doses of 100 .mu.g/kg the hormone significantly potentiates the hypnosis produced by the benzodiazepines. Apparently the interactions described may be the result of a modification of possible changes in cholinergic activity caused by the benzodiazepines. Although as yet no **unequivocal** explanation can be offered for the different effects, the observations may explain the highly contradictory findings of other authors in both animal and human studies.

L132 ANSWER 18 OF 45 HCAPLUS COPYRIGHT 2000 ACS
AN 1984:63004 HCAPLUS
DN 100:63004
TI Comparison of the effects of methyl n-butyl ketone and phenobarbital on rat liver cytochrome P 450 and the metabolism of chloroform to phosgene
AU Branchflower, Richard V.; Schulick, Richard D.; George, John W.; Pohl, Lance R.
CS Lab. Chem. Pharmacol., Natl. Heart, Lung, and Blood Inst., Bethesda, MD, 20205, USA
SO Toxicol. Appl. Pharmacol. (1983), 71(3), 414-21
CODEN: TXAPA9; ISSN: 0041-008X
DT Journal
LA English
AB The treatment of rats with Me Bu ketone (MBK) [591-78-6] produced qual. changes in the compn. of microsomal cytochrome P 450 [9035-51-2] in rat liver. The degree of the chromatog. changes paralleled the effect of MBK on the rate of metab. of CHCl3 [67-66-3] to COCl2 [75-44-5] and CHCl3-induced hepatotoxicity, suggesting that MBK potentiated the hepatotoxicity of CHCl3, at least in part, by inducing the formation of cytochromes P 450 that metabolized CHCl3 to the hepatotoxin COCl2. Reconstitution studies with a form of cytochrome P 450 isolated from liver microsomes of rats treated with MBK or phenobarbital (PB) [**50-06-6**] showed **unequivocally** that cytochrome P 450 can metabolize CHCl3 to COCl2. Although anal. of rat liver microsomes by SDS-polyacrylamide electrophoresis and anion-exchange chromatog. suggested that MBK and PB had similar effects on the compn. of cytochromes P 450, metab. studies indicated that differences did exist.

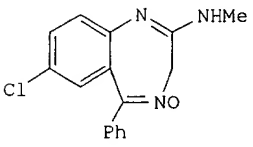
L132 ANSWER 19 OF 45 HCAPLUS COPYRIGHT 2000 ACS
AN 1983:569874 HCAPLUS
DN 99:169874
TI Induction of midcycle gonadotropin surge by ovarian steroids in women: a critical evaluation
AU Liu, J. H.; Yen, S. S. C.
CS Sch. Med., Univ. California, San Diego, La Jolla, CA, 92093, USA
SO J. Clin. Endocrinol. Metab. (1983), 57(4), 797-802
CODEN: JCEMAZ; ISSN: 0021-972X
DT Journal
LA English
GI



I

AB A preovulatory configuration of estradiol (I)(E2) [50-28-2] and progesterone (P4) [**57-83-0**] levels was achieved during the midfollicular phase of normal women and in hypogondal women (with E2 implants) by stepwise incremental infusions of E2 and P4. During the 96 h of E2 infusion alone, reproducible and concomitant surges of LH [9002-67-9] and FSH [9002-68-0] occurred after latency periods of 58 and 68.2 h in midfollicular and hypogonadal subjects, resp. The mean duration of the E2-induced surge was shorter for both normal midfollicular (22.7 h) and hypogonadal women (21.8 h) than was the spontaneous midcycle surge (48 h). When P4 infusion was superimposed 48 h after the initiation of E2 infusion, a LH-FSH surge that approximated the dimension of the spontaneous surge was achieved in both groups of women. For the hypogonadal women, but not midfollicular women, P4 infusion also advanced the surge onset by 14.7 h. These data represent the 1st **unequivocal** demonstration that incremental E2 sustained for .apprx.60 h constitutes the ovarian signal for initiating the midcycle gonadotropin surge and that a small increment of P4 secreted by the preovulatory follicle is required to establish the normal dimension of the surge. Thus, P4, although essential for creating a normal gonadotropic surge, operates by synergizing the obligatory action of E2.

L132 ANSWER 20 OF 45 HCAPLUS COPYRIGHT 2000 ACS
AN 1983:498692 HCAPLUS
DN 99:98692
TI Experimental induction of benzodiazepine tolerance and physical dependence
AU Ryan, Gary P.; Boisse, Norman R.
CS Coll. Pharm. Allied Health Prof., Northeast. Univ., Boston, MA, 02115, USA
SO J. Pharmacol. Exp. Ther. (1983), 226(1), 100-7
CODEN: JPETAB; ISSN: 0022-3565
DT Journal
LA English
GI

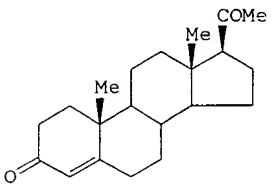


I

AB To initiate studies of benzodiazepine tolerance and phys. dependence, a reproducible animal model was developed utilizing chlordiazepoxide (I) [**58-25-3**] in rats. Based on the chronically equiv. dosing principle, a regimen was devised to maintain rats in a state of quantifiable intoxication for 5 wk. Chlordiazepoxide was delivered intragastrically on a twice-daily basis in doses individually adjusted day-to-day and animal-to-animal to produce an equiv. impairment of motor function evaluated by a gross neurol. screen. Quant. anal. of central nervous system depression ratings during the time of peak effect (4 h postdose) confirmed that the criterion of chronic equivalence was indeed met. Over the 5-wk period of repeated dosing, tolerance was reflected in a 5-fold increase in maintenance dose, from 163.3 mg/kg on day 2 to 839.3 mg/kg on day 35. Tolerance developed more rapidly during the 1st 9-10 days but continued to develop thereafter more slowly without apparent

ceiling. Upon abrupt withdrawal, a syndrome of hyperexcitation developed. Signs included twitches, tremors, muscle hypertonus, arched back, piloerection, myoclonic jerks, augmented struggle and **vocalization** upon handling, increased startle response, tail erection, teeth chatter, blanched ears, and wt. loss. No spontaneous convulsions occurred. Latency to onset of withdrawal ranged 2-5 days; signs peaked in intensity in 8 days and had disappeared by 14 days posttreatment. This animal model appears to provide a useful tool for the study of specific mechanisms underlying benzodiazepine tolerance and phys. dependence.

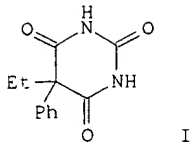
L132 ANSWER 21 OF 45 HCAPLUS COPYRIGHT 2000 ACS
AN 1983:482742 HCAPLUS
DN 99:82742
TI Close correlation between progesterone receptor concentration and hormonal sensitivity in DMBA-induced mammary tumors of the rat
AU Mobbs, B. G.
CS Dep. Surg., Univ. Toronto, Toronto, ON, M5S 1A8, Can.
SO Eur. J. Cancer Clin. Oncol. (1983), 19(6), 835-42
CODEN: EJCODS; ISSN: 0277-5379
DT Journal
LA English
GI



I

AB Cyclic administration of estrogen alone and with progesterone (I) [**57-83-0**] to ovariectomized rats bearing DMBA [57-97-6]-induced tumors resulted in more uniform cytosol estrogen and I receptor (ER and PgR) concns. in the uteri and a stronger correlation between ER and PgR concns. in the tumors than in a group of naturally cycling animals. Using this model, the concn. of PgR was a better indicator of tumor response to ovariectomy and hormonal restimulation than the concn. of ER. In 10 **unequivocally** responsive adenocarcinomas, receptor values, expressed as fmol/mg cytosol protein, were: ER 47, PgR 246, PgR:ER 5.9, compared with ER 18, PgR 33, and PgR:ER 1.8 in 3 autonomous adenocarcinomas. All 3 parameters were different between the 2 groups, but there was overlap in the ER values, whereas no overlap occurred in the PgR values or the PgR:ER ratios. Ten other adenocarcinomas showed a different sensitivity to restimulation than to ovariectomy and 6 tumors were fibroadenomas or of mixed histopathol. For the whole tumor population the response to hormonal restimulation at the time of excision suggested that a PgR concn. >60 fm/mg protein combined with an ER concn. >20 fm/mg protein is necessary for the maintenance of hormonal sensitivity. Using these criteria, response was related to receptor concns. in 93% of the tumors.

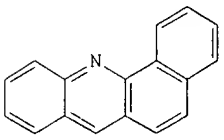
L132 ANSWER 22 OF 45 HCAPLUS COPYRIGHT 2000 ACS
AN 1983:482010 HCAPLUS
DN 99:82010
TI Transcriptional regulation of rat liver epoxide hydratase, NADPH-cytochrome P-450 oxidoreductase, and cytochrome P-450b genes by phenobarbital
AU Hardwick, James P.; Gonzalez, Frank J.; Kasper, Charles B.
CS McArdle Lab. Cancer Res., Univ. Wisconsin, Madison, WI, 53706, USA
SO J. Biol. Chem. (1983), 258(13), 8081-5
CODEN: JBCHA3; ISSN: 0021-9258
DT Journal
LA English
GI



I

AB The relative rates of transcription of epoxide hydratase [9048-63-9], NADPH-cytochrome P 450 oxidoreductase [9039-06-9], and cytochrome P-450 b [9035-51-2] genes were detd. in purified hepatocyte nuclei isolated at different times after phenobarbital (I) [**50-06-6**] administration. The rates of transcription of the epoxide hydratase and oxidoreductase genes were increased 4- and 9-fold, resp., above control levels 1 h after administration of the drug. Transcription rates for the oxidoreductase gene slowly decreased to control values at 24 h while transcription of the epoxide hydratase gene rapidly declined to approx. 2-fold above control values at 2.5 h and remained at this level up to 24 h after administration. Transcription of the cytochrome P-450b gene followed a markedly different induction time course than the epoxide hydratase and oxidoreductase genes. Specifically, cytochrome P-450b gene transcription increased 23-fold above control values 6 to 8 h after phenobarbital administration and then slowly declined to 14-fold at 24 h. The increased levels of intranuclear pre-mRNA and cytoplasmic mRNA for each enzyme correlated well with transcriptional activity. In contrast to these results, the rate of transcription of the serum albumin gene was not affected, and levels of albumin mRNA actually decreased after administration of phenobarbital. The rapid increase in the rates of transcription and the appearance of elevated levels of nuclear pre-mRNAs and cytoplasmic mRNAs **unequivocally** demonstrates that phenobarbital elevates levels of these drug-metabolizing enzymes primarily by augmenting the rate of transcription of their resp. genes.

L132 ANSWER 23 OF 45 HCAPLUS COPYRIGHT 2000 ACS
AN 1983:66848 HCAPLUS
DN 98:66848
TI On the metabolic activation of benz[a]acridine and benz[c]acridine by rat liver and lung microsomes
AU Jacob, Juergen; Schmoldt, Achim; Kohbrok, Wolfgang; Raab, Gottfried; Grimmer, Gernot
CS Biochem. Inst. Umweltcarcinogene, Ahrensburg, Univ. Hamburg, Hamburg, Fed. Rep. Ger.
SO Cancer Lett. (Shannon, Irel.) (1982), 16(3), 297-306
CODEN: CALEDQ; ISSN: 0304-3835
DT Journal
LA English
GI

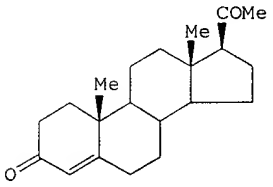


I

AB The metab. of benz[a]- [225-11-6] and benz[c]acridine (I) [225-51-4] by liver and lung microsomes from untreated, phenobarbital [**50-06-6**]-treated, and benzo[k]fluoranthene (BkF) [207-08-9]-treated rats was studied by gas chromatog./mass spectrometry. Epoxidn. and hydrolysis of the epoxides to dihydrodiols were the predominant pathways for all substrates. N-Oxidn. is likely to occur in the case of I. However, no **unequivocal** evidence could be obtained for the formation of the ultimate carcinogens, the trans-3,4-dihydrodiol-1,2-epoxides, in the case of both benz[a]acridine and I. K-region oxidn. was induced by phenobarbital, whereas the formation of non-K-region metabolites increased

after BkF treatment in the case of I.

L132 ANSWER 24 OF 45 HCAPLUS COPYRIGHT 2000 ACS
AN 1982:538921 HCAPLUS
DN 97:138921
TI In vitro progesterone stimulates the release of luteinizing hormone-releasing hormone from superfused hypothalamic tissue from ovariectomized estradiol-primed prepuberal rats
AU Kim, K.; Ramirez, V. D.
CS Dep. Physiol. Biophys., Univ. Illinois, Urbana, IL, 61801, USA
SO Endocrinology (Baltimore) (1982), 111(3), 750-7
CODEN: ENDOAO; ISSN: 0013-7227
DT Journal
LA English
GI



I

AB The effect of in vitro progesterone (I) [**57-83-0**] on the LH-RH [9034-40-6] app. in hypothalamic fragments from ovariectomized, estradiol-primed rats was examd. Immature, 28-day-old female rats were ovariectomized and implanted with silastic capsules contg. estradiol. At 30 days, the animals were decapitated, and the mediobasal hypothalamic-anterior hypothalamic-preoptic area fragments were removed and transferred to superfusion chambers. These hypothalamic units received I delivered either in pulses (10 min on, 20 min off; 10 ng/mL) or in a continuous mode. LH-RH was detd. in perfusates and postsuperfusion tissues by RIA. The intermittent mode of I administration **unequivocally** stimulated episodic LH-RH release. A maximal stimulatory effect of I (close to a 4-fold increment over pretreatment levels) was obsd. about 1 h after initial I administration. After a decline in LH-RH release to approx. initial levels, it took about 1 h more for the intermittent I pulses to once again stimulate the LH-RH secretory app. In contrast to the intermittent mode, continuous I infusions were not effective in increasing LH-RH release. The release profile was sustained at a stable low level without any pulsatile fluctuation. Intermittent superfusion of hypothalamic fragments with cholesterol did not stimulate LH-RH release. A single I pulse of 10-min duration augmented the LH-RH release rate (>150% increment over pretreatment levels), while that of 1-min duration and similar strength (10 ng/mL) failed to change the LH-RH release rate. The stimulatory effectiveness of I on the LH-RH release rate in vitro was reduced when hypothalamic units were superfused at 30.degree. instead of 37.degree. and was not present in hypothalamic fragments from intact prepuberal rats. Thus, in vitro intermittent infusion of I, but not a continuous administration, can directly activate the neural LH-RH secretory app. of hypothalamic fragments from ovariectomized, estradiol-primed prepuberal rats.

L132 ANSWER 25 OF 45 HCAPLUS COPYRIGHT 2000 ACS
AN 1982:520776 HCAPLUS
DN 97:120776
TI Control of corpus luteum function during the second half of pregnancy in the rat: a direct relationship between conceptus number and both serum and ovarian relaxin levels
AU Golos, Thaddeus G.; Sherwood, O. D.
CS Sch. Basic Med. Sci., Univ. Illinois, Urbana, IL, 61801, USA
SO Endocrinology (Baltimore) (1982), 111(3), 872-8
CODEN: ENDOAO; ISSN: 0013-7227
DT Journal
LA English

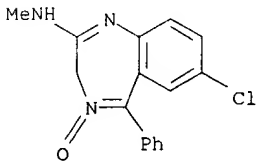
AB The effects of conceptus or fetus removal on several parameters of luteal activity (serum and ovarian relaxin [9002-69-1] immunoactivity levels, serum progesterone [**57-83-0**] immunoactivity levels, and corpus luteum wts.) were investigated during the second half of pregnancy in the rat. Conceptuses were aspirated from the uteri of pregnant rats on day 8 of pregnancy so that they carried 0, 1, 2, 5, and 10 or more conceptuses until they were autopsied on day 10, 12, 14, 16, 18, or 20 of pregnancy. A direct relation existed between the no. of conceptuses and the rate and(or) degree of increase in all of the parameters of corpus luteum activity. The conceptuses had no local effect on ovarian relaxin levels or on luteal wts. when the conceptus side ovary was compared with the nonconceptus side ovary. In pregnant rats in which all but 2 fetuses were removed (all placentas were left undisturbed), there were no differences on days 18 or 20 in any parameter of corpus luteum activity between fetectomized and sham-operated rats. Apparently, the placenta plays the dominant role in the regulation of all of the above parameters of corpus luteum activity during the 2nd half of pregnancy in the rat. The specific factor(s) or mechanism(s) by which the placenta promotes relaxin synthesis, progesterone secretion, and corpus luteum growth have yet to be clearly and **unequivocally** characterized in the rat. The fact that conceptus no. and the rate and(or) degree of increase of all of the parameters of luteal activity measured from day 12 through day 18 are directly related is consistent with the possibility that the placental support of these activities is mediated through a common mechanism during this period in the rat.

L132 ANSWER 26 OF 45 HCAPLUS COPYRIGHT 2000 ACS
AN 1982:486114 HCAPLUS
DN 97:86114
TI Female sex behaviors in the South African clawed frog, Xenopus laevis: gonadotropin-releasing, gonadotropic, and steroid hormones
AU Kelley, Darcy B.
CS Dep. Psychol., Princeton Univ., Princeton, NJ, 08544, USA
SO Horm. Behav. (1982), 16(2), 158-74
CODEN: HOBEAO; ISSN: 0018-506X
DT Journal
LA English
AB Sex behaviors of female South African clawed frogs (X. laevis) were characterized and the behavioral effects of endocrine manipulation were obsd. The responses of females to clasp assaults by sexually active males were obsd. Two patterns of female responses predominated. In one, females exhibited extreme leg extension and ticking **vocalizations** when clasped (unreceptive behaviors). In the other, females responded to being clasped by adduction of the thighs and increased flexion at the knee; ticking **vocalizations** were absent (receptive behaviors). In intact females, injection of human chorionic gonadotropin (HCG) [9002-61-3] or LH-RH [9034-40-6] into the dorsal lymph sac increased receptivity. These hormones do not promote receptivity in ovariectomized females. Neither estradiol (E) [50-28-2] nor progesterone (P) [**57-83-0**] when administered alone was effective in restoring receptivity to ovariectomized females. In combination, E + P increased sexual receptivity. LH-RH, when given to ovariectomized, E + P-treated females, further increased receptivity and led to the prolonged amplexus otherwise obsd. with an HCG-injected intact female. The behavioral effects of LH-RH may be independent of action on the pituitary since they are not mimicked by gonadotropin.

L132 ANSWER 27 OF 45 HCAPLUS COPYRIGHT 2000 ACS
AN 1981:215 HCAPLUS
DN 94:215
TI Irreversible inhibitors of GABA transaminase induce antinociceptive effects and potentiate morphine
AU Buckett, W. R.
CS Cent. Rech. Merrell Int., Strasbourg, 67084, Fr.
SO Neuropharmacology (1980), 19(8), 715-22
CODEN: NEPHBW; ISSN: 0028-3908
DT Journal
LA English
AB .gamma.-Acetylenic GABA (I) [57659-38-8] and .gamma.-vinyl GABA (II) [60643-86-9] (i.p.) had antinociceptive effects unaccompanied by ataxia in

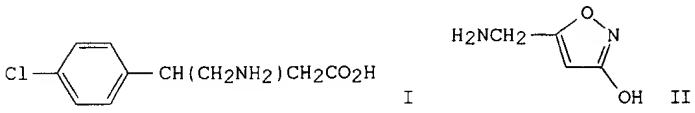
mice on the 52.degree. hot-plate test, and in rats in a tail-stimulation procedure, which were maximal after 4-6 h, correlating temporally with reported max. increases of brain GABA [56-12-2]. This effect was antagonized by a subconvulsive dose of bicuculline [**485-49-4**] (0.5 mg/kg, i.p.) in rats, but not by naloxone-HCl [357-08-4] (1 mg/kg, i.p.) in mice. Only the (+)-stereoisomer of II, active as a GABA-transaminase [9037-67-6] inhibitor, was antinociceptive. The effects appeared to be causally related to elevated cerebral GABA levels. The profile of I and II in the tail-stimulation test suggested a specific antinociceptive effect since **vocalization** and **vocalization** after-discharge were similarly affected. I and II enhanced morphine-HCl [52-26-6] analgesia 5 h after administration, and did not affect the naloxone-pptd. morphine withdrawal syndrome. Thus, I and II may have distinct antinociceptive effects in rats and mice related to increased brain GABA levels, but which are not opioid-like in nature.

L132 ANSWER 28 OF 45 HCAPLUS COPYRIGHT 2000 ACS
AN 1980:423576 HCAPLUS
DN 93:23576
TI The neurochemical control of crying
AU Panksepp, Jaak; Meeker, Rick; Bean, N. Jay
CS Dep. Psychol., Bowling Green State Univ., Bowling Green, OH, 43403, USA
SO Pharmacol., Biochem. Behav. (1980), 12(3), 437-43
CODEN: PBBHAU; ISSN: 0091-3057
DT Journal
LA English
AB The capacity of 18 drugs, including those which modify brain opioid, serotonin, norepinephrine, dopamine, and acetylcholine activity, to modulate sepn.-induced distress vocalizations (DV) in young chicks were studied. I.p. morphine (1.7-5 mg/kg) injections were very effective in reducing DV's, and naloxone (1.7-5.0 mg/kg) also increased DV's. Smaller bidirectional effects were also obsd. after pharmacol. manipulation of cholinergic and serotonergic systems. Blockade of these systems with atropine (5-15 mg/kg) and methylsergide (0.56 mg/kg) increased DV's, whereas a facilitation of activity in these systems with pilocarpine (15 mg/kg) and quipazine (15 mg/kg) reduced DV's. Small redns. of DV's could also be achieved with neuroleptics such as haloperidol and chlorpromazine and with apomorphine, suggesting that redn. of brain dopamine activity reduces DV's, whereas clonidine (0.56-1.7 mg/kg) was very powerful in reducing DV's, perhaps through autoreceptor redn. of brain NE activity. Chlordiazepoxide (5-15 mg/kg) was capable of reducing DV's, whereas imipramine (15-45 mg/kg) and pentobarbital (5-15 mg/kg) were essentially without effect. Opiate effects could be obtained as readily following intraventricular as following peripheral drug administration, whereas cholinergic and serotonergic agents were most effective by the peripheral route. The opiate system had the most powerful specific effect on distress vocalization of all systems studied.
IT **58-25-3**
RL: BIOL (Biological study)
(distress **vocalization** response to)
RN 58-25-3 HCAPLUS
CN 3H-1,4-Benzodiazepin-2-amine, 7-chloro-N-methyl-5-phenyl-, 4-oxide (9CI) (CA INDEX NAME)



L132 ANSWER 29 OF 45 HCAPLUS COPYRIGHT 2000 ACS
AN 1980:208952 HCAPLUS
DN 92:208952
TI Antinociceptive effects of baclofen and muscimol upon intraventricular administration

AU Liebman, Jeffrey M.; Pastor, Gary
CS Res. Dep., Ciba-Geigy Corp., Summit, NJ, 07901, USA
SO Eur. J. Pharmacol. (1980), 61(3), 225-30
CODEN: EJPHAZ; ISSN: 0014-2999
DT Journal
LA English
GI

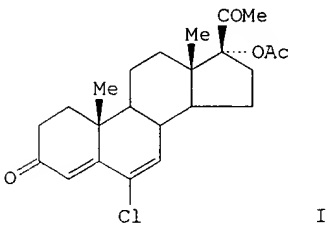


I

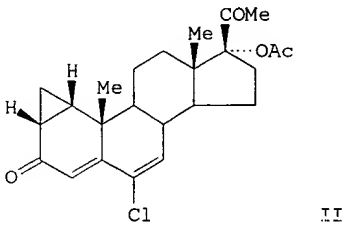
II

AB The effects of intraventricularly administered dl-baclofen (I) [**62594-36-9**] and muscimol (II) [2763-96-4] were investigated on tail-flick responding and on **vocalization** and motor responses to nociceptive pinch. I (1 .mu.g) and II (0.1 .mu.g) strongly reduced responding to pinch, particularly **vocalization**, without altering tail-flick responding. When given systemically, however, I markedly attenuated tail-flick as well as pinch responding. II produced only weak antinociception by systemic administration, suggesting that it may have poor access to brain. At antinociceptive doses, intraventricular II produced less apparent muscle relaxation than did I. Thus, the antinociceptive action of I may be mediated in part by a supraspinal, GABAergic substrate, in addn. to a spinal component which may not directly involve GABA.

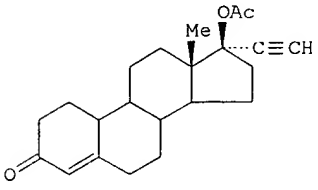
L132 ANSWER 30 OF 45 HCAPLUS COPYRIGHT 2000 ACS
AN 1980:122294 HCAPLUS
DN 92:122294
TI The progestational activity of different gestagens used for human contraception in the beagle bitch
AU Beier, S.; Haase, F.; Kosub, B.; Duesterberg, B.; Elger, W.
CS Res. Lab., Schering A.-G., Berlin, Fed. Rep. Ger.
SO Contraception (1979), 20(6), 533-48
CODEN: CCPTAY; ISSN: 0010-7824
DT Journal
LA English
GI



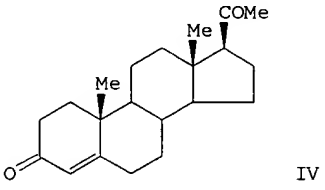
I



II



III

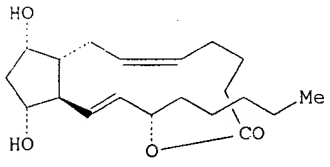


IV

AB In long-term studies chlormadinone acetate (I) [302-22-7] and cyproterone

acetate (II) [427-51-0] had much more pronounced mammotropic effects in dogs than norethisterone acetate (III) [51-98-9] or levonorgestrel (LN) [6533-00-2]. To evaluate gestagenic potency of these compds. in dogs as a potential determinant of these substance differences, a quant. canine gestagen bioassay was developed. Ovariectomized adult beagles were sequentially treated with 30 .mu.g estradiol (E2)/day, s.c. for 15 days and gestagen (s.c., orally) + 3 .mu.g E2/day, s.c. days 16-29. This regimen was optimal for endometrial gestagen effects. According to their s.c. transformatory potency in day 29 endometrial biopsies, the compds. could be ranked as follows: progesterone (IV) [**57-83-0**] < III < LN = I = II. The corresponding threshold doses (TD s.c.) were 3.0-10.0, 1.0, 0.1-0.3, 0.1-0.3 and 0.3 mg/day. A different rank was found after oral administration: III < IV (s.c.) < LN < I = II. The corresponding oral TD were .gtoreq.30.0, 3.0-10.0, 1.0, 0.1 and 0.1 mg/day. Related to IV, LN and III had a much lower gestagenic potency in dogs than in humans. The opposite is true for I and II. The low oral activity of III and LN in dogs points to an important first liver passage metab. of both compds. in this species. Serum detns. substantiated the very low or high oral bioavailability in case of LN, III and II. Clin., by the oral route of administration, there was no doubt that I is markedly less potent than III which itself is less potent than LN whereas in the dogs, I is **unequivocally** the most potent of the progestagens under consideration. This implies that dogs are overdosed with several human multiples when I is administered and probably underdosed with III, at least on a comparative basis.

L132 ANSWER 31 OF 45 HCAPLUS COPYRIGHT 2000 ACS
AN 1979:469012 HCAPLUS
DN 91:69012
TI Comparison of the lytic effects of four prostaglandin analogs in the chacma baboon (Papio ursinus ursinus)
AU Rall, H. J. S.; Zuurmond, T. J.; Weidemann, A.
CS Dep. Obstet. Gynaecol., Tygerberg Hosp., Tygerberg, 7505, S. Afr.
SO Int. J. Fertil. (1979), 24(1), 21-6
CODEN: INJFA3; ISSN: 0020-725X
DT Journal
LA English
GI

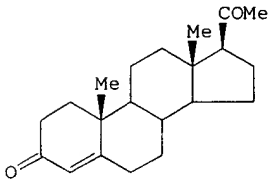


I

AB Six healthy, cycling female chacma baboons (P. ursinus ursinus) were used to det. the luteolytic effects of 4 prostaglandin analogs. Five to 7 days following ovulation, venous blood was collected and the baboon given a single i.m. injection of a compd. at a recommended dose. Blood was then collected serially every 3 h for 3 samples and again at 24, 48, and 72 h to det. the continued effect of the prostaglandin analogs on corpus luteum prodn. of progesterone [**57-83-0**]. PGF2.alpha. 1,15-lactone (I) [55314-49-3], 11.alpha.(15S)-17-phenyl-18,19,20-trinor-ent-PGE2 Me ester [53232-36-3], and 17-phenyl-18,19,20-trinor-PGF2.alpha. [38344-08-0] exhibited definite luteolytic potential in this species. **Equivocal** results were obtained with (15S)-15-methyl-PGF2.alpha. THAM [58551-69-2] and its toxic qualities resulted in the death of 3 animals.

L132 ANSWER 32 OF 45 HCAPLUS COPYRIGHT 2000 ACS
AN 1978:485105 HCAPLUS
DN 89:85105
TI Influence of gonadal hormones and sexual behavior on ultrasonic vocalization in rats: I. Treatment of females
AU Geyer, Lynette A.; Barfield, Ronald J.

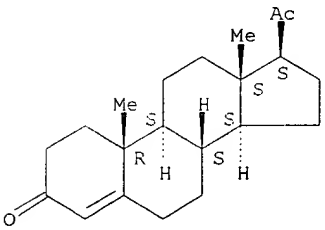
CS Livingston Coll., Rutgers, State Univ., New Brunswick, N. J., USA
SO J. Comp. Physiol. Psychol. (1978), 92(3), 438-46
CODEN: JCPPAV; ISSN: 0021-9940
DT Journal
LA English
GI



I

AB Ultrasonic **vocalizations** were measured when male rats were placed with ovariectomized females that had experienced various hormonal and behavioral treatments. In 1 expt., 18 males were tested with females in each of the following conditions: nonestrous ovariectomized (OVX), estrogen-treated (E), estrogen and progesterone (I) [**57-83-0**]-treated (EP), and estrogen and I-treated and given 2 intromissions from a stud male prior to testing (EPI). Control conditions included clean cage (CL) and cage soiled by an estrous female (SOI). The treatments differed in effect on rate and maintenance of **vocalization**: EP >E >EPI = OVX >SOI >CL. In tests in which males produced a high rate of **vocalization**, some males with short intromission latencies shifted from the normal 50 kHz pulse to a 22 kHz pulse. In a 2nd expt., the effect of the female's **vocalization** and movement on the rate of and latency to **vocalization** was measured. Twenty-one males were presented with each of the following stimulus conditions: estrous female with red light (EP), estrous female without red light (EP dark), estrous anesthetized female (EP anes), and nonestrous ovariectomized anesthetized female (OVX anes). Effects on **vocalization** of various treatments were as follows: EP = EP dark >EP anes >OVX anes. Apparently, the 50 kHz **vocalizations** constitute a graded response influenced by the female's hormonal and sexual condition.
IT **57-83-0**, biological studies
RL: BIOL (Biological study)
(**vocalization** response to sex activity and)
RN 57-83-0 HCAPLUS
CN Pregn-4-ene-3,20-dione (9CI) (CA INDEX NAME)

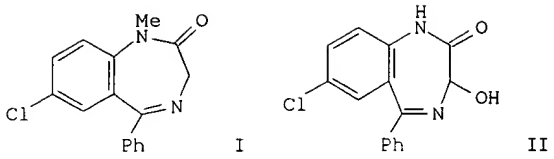
Absolute stereochemistry.



L132 ANSWER 33 OF 45 HCAPLUS COPYRIGHT 2000 ACS
AN 1978:131095 HCAPLUS
DN 88:131095
TI On the acute effect of some drugs on higher nervous activity in man followed up by the laboratory language method
AU Hrbek, Jan.; Komenda, S.; Macakova, J.; Siroka, A.; Dostalova, K.
CS Med. Fac., Palacky Univ., Olomouc, Czech.
SO Act. Nerv. Super. (1977), 19(4), 294-5
CODEN: ACNSAX; ISSN: 0001-7604

?

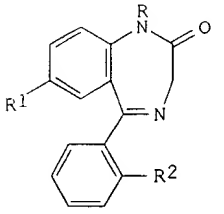
DT Journal
LA English
GI



I II

AB In healthy volunteers diazepam (I) [439-14-5] and oxazepam (II) [**604-75-1**] (10 and 20 mg, resp.) inhibited artificial conditioned **speech** reflexes esp. when they were established by complex tactile assocns. Chlordiazepoxide [**58-25-3**] (30 mg) and medazepam [2898-12-6] (5-15 mg) had no effect.

L132 ANSWER 34 OF 45 HCAPLUS COPYRIGHT 2000 ACS
AN 1978:115428 HCAPLUS
DN 88:115428
TI A repeated dose comparison of three benzodiazepine derivatives (nitrazepam, flurazepam and flunitrazepam) on subjective appraisals of sleep and measures of psychomotor performance the morning following night-time medication
AU Hindmarch, Ian
CS Dep. Psychol., Univ. Leeds, Leeds, Engl.
SO Acta Psychiatr. Scand. (1977), 56(5), 373-81
CODEN: APYSA9; ISSN: 0001-690X
DT Journal
LA English
GI

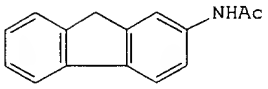


I, R=R^2=H, R^1=NO_2
II, R=$CH_2CH_2NEt_2$, R^1=Cl, R^2=F
III, R=Me, R^1=NO_2, R^2=F

AB Repeated doses of 5 mg nitrazepam (I) [146-22-5], 15 mg flurazepam (II) [**17617-23-1**], and 1 mg flunitrazepam (III) [**1622-62-4**] improved subjective assessments of the ease of getting to sleep and the perceived quality of induced sleep in 30 healthy volunteers. The subjective reports of improved sleep inducement were related to a perceived difficulty in awakening from sleep the morning after medication. This subjectively reported hangover was also shown in the impairment of mental arithmetic abilities as measured on the serial subtraction of sevens technique. However, complex psychomotor performance was unaffected by repeated administration of these 3 benzodiazepine derivs., although these later results were somewhat **equivocal**. Evidence of a rebound phenomenon after 4 nights' withdrawal of active medication was shown in both subjective and objective measures of sleep and early morning behavior.

L132 ANSWER 35 OF 45 HCAPLUS COPYRIGHT 2000 ACS
AN 1978:100127 HCAPLUS
DN 88:100127
TI Drug-induced enhancement of hepatic tumorigenesis

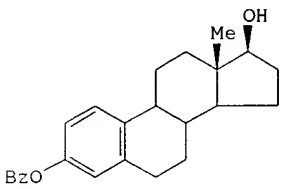
AU Peraino, C.; Fry, R. J. M.
CS Argonne Natl. Lab., Argonne, Ill., USA
SO Report (1977), CONF-770342-1, 25 pp. Avail.: NTIS
From: Energy Res. Abstr. 1977, 2(21), Abstr. No. 53167
DT Report
LA English
GI



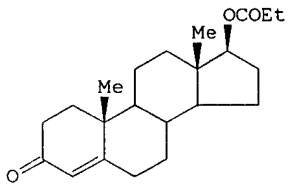
I

AB Epidemiol. evidence suggests that the human population is exposed to environmental agents that increase the risk of cancer. The 2-stage or initiation-promotion model of tumorigenesis raises the possibility that such environmental agents may comprise both carcinogens and substances that are not carcinogens themselves but instead enhance the tumorigenic effects of brief exposures to low levels of carcinogens. Studies on rats showed that dietary phenobarbital [**50-06-6**] enhances liver tumorigenesis initiated by the prior feeding of the carcinogen, 2-acetylaminofluorene (I) [53-96-3]. Phenobarbital is a well known stimulator of liver growth but its effects are reversible, and thus far there is no **unequivocal** evidence that phenobarbital is tumorigenic. Other agents that influence liver growth and metab. to varying degrees were also tested.

L132 ANSWER 36 OF 45 HCAPLUS COPYRIGHT 2000 ACS
AN 1978:16455 HCAPLUS
DN 88:16455
TI Ejaculatory and postejaculatory behavior of male and female rats: effects of sex hormones and electric shock
AU Barfield, Ronald J.; Krieger, Monica Schoelch
CS Dep. Biol., Livingston Coll., New Brunswick, N. Y., USA
SO Physiol. Behav. (1977), 19(2), 203-8
CODEN: PHBHA4
DT Journal
LA English
GI



I

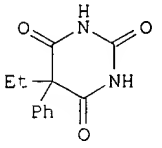


II

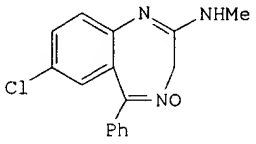
AB Ejaculatory patterns were obsd. in normally reared, postpuberally castrated male and female rats treated with sex hormones and elec. shock in adulthood. Three females treated with 50 .mu.g estradiol benzoate (I) [50-50-0] and 500 .mu.g progesterone (II) [**57-83-0**] showed intromission and ejaculatory behavior when subjected to shock. Refractory periods were abnormally short and there was almost no postejaculatory **vocalization**. In 1 expt., males and females were tested with elec. shock following daily treatment with 32 .mu.g I with and without 500 .mu.g II on the test day. There was no difference between males and females in preejaculatory behavior, but females displayed abbreviated refractory periods and no postejaculatory **vocalization**. II had no obsd. effect. When castrated males and females were subjected to shock after treatment with 8 .mu.g I/day for 3 weeks and no II was given, females showed drastically decreased refractory periods and little **vocalization**. Males and females treated with testosterone

propionate (III) [57-85-2] and shock displayed ejaculatory patterns, normal refractory periods, and **vocalization**. Apparently, female rats are capable of exhibiting the ejaculatory response without sex hormone treatment in perinatal life or androgen treatment in adulthood. It was also demonstrated that there is a sex difference in the postejaculatory behavior shown by estrogen-treated male and female rats.

L132 ANSWER 37 OF 45 HCAPLUS COPYRIGHT 2000 ACS
AN 1977:165968 HCAPLUS
DN 86:165968
TI Gas-chromatographic analysis of some drugs in samples of biological liquids with a rubidium bromide thermionic detector
AU Banelli, Giorgio; Marini, Pietro
CS Lab. Chim. Prov., Arezzo, Italy
SO Boll. Chim. Unione Ital. Lab. Prov. (1976), 2(11), 310-17
CODEN: BCIPDD
DT Journal
LA Italian
GI



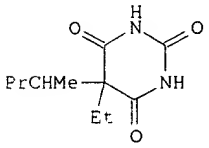
I



II

AB Barbiturates, benzodiazepines, and methaqualone [72-44-6], drugs frequently taken in overdose, could be identified and detd. at 3-5 .mu.g/mL in biol. fluids by means of gas chromatog., using a RbBr thermionic detector, after simple extn. without cleanup. Phenobarbital (I) [**50-06-6**], pentobarbital [57-33-0], and barbital [57-44-3] were detd. in whole blood, serum, urine, and gastric washings by extn. with CHCl3 at acid pH, methylation with CH2N2, and gas chromatog. The benzodiazepines chlordiazepoxide (II) [**58-25-3**], diazepam [439-14-5], and flurazepam [**17617-23-1**], as well as methaqualone, were detd. in whole blood, serum, and gastric washings by extn. with CHCl3 at pH 9 and chromatog.; alk. exts. of urine gave too many extraneous peaks to be analyzed by this method. Also, nitrazepam [146-22-5] could not be eluted from the column in sufficient amts. to be detectable. If accompanied by confirmatory tests such as thin-layer chromatog., this procedure can give **uniquivocal** information on the type and amt. of compd. ingested.

L132 ANSWER 38 OF 45 HCAPLUS COPYRIGHT 2000 ACS
AN 1976:115866 HCAPLUS
DN 84:115866
TI Barbiturate withdrawal-induced delayed aggression
AU Singh, Jasbir M.; Puente, Raquel; Sacco, Therese M.; Singh, Melbra D.
CS Alcohol. Serv. Unit, Charity Hosp., New Orleans, La., USA
SO Drug Addict. (1974), 3, 81-7
CODEN: DRADDU
DT Journal
LA English
GI



I

AB Pentobarbital (I) [**76-74-4**] withdrawal from addicted rats

decreased rectal temp., and caused tremors, hyperirritability, **vocalization** on handling, and mild aggression. These behavioral changes were intensified by reserpine [50-55-5] and d-amphetamine sulfate [51-63-8]. The enhancement of these behavorial changes was prevented to some extent (60-70%) by treatment with chlorpromazine [50-53-3] or its metabolite 7-hydroxychlorpromazine [2095-62-7].

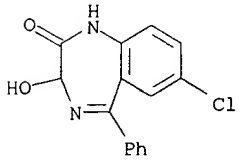
L132 ANSWER 39 OF 45 HCAPLUS COPYRIGHT 2000 ACS
AN 1975:491424 HCAPLUS
DN 83:91424
TI Assessment of possible luteolytic effect of intraovarian injection of prostaglandin F2.alpha. in the human
AU Korda, Andrew R.; Shutt, Donald A.; Smith, Ian D.; Shearman, Rodney P.; Lyneham, Robert C.
CS Queen Elizabeth II Res. Inst. Mothers Infants, Univ. Sydney, Sydney, Aust.
SO Prostaglandins (1975), 9(3), 443-9
CODEN: PRGLBA
DT Journal
LA English
GI For diagram(s), see printed CA Issue.
AB In patients awaiting laparoscopic tubal diathermy, injection of PGF2.alpha. (I) [551-11-1] 5-8 days after LH peak into the corpus luteum, adjacent stroma, or intermediate ovarian structure had no effect on peripheral plasma progesterone [**57-83-0**] levels or uterine bleeding. An injection of 500 or 1000 .mu.g I given **unequivocally** into the corpus luteum produced a rapid and profound decrease in plasma progesterone levels, the nadir coinciding with the onset of uterine bleeding which commenced 24 hr after the injection and persisted for more than 7 days. Injection of 100 .mu.g in the same vol. of saline had no such effect. Despite continued bleeding plasma progesterone levels returned to normal levels for 3 days and then decreased again.

L132 ANSWER 40 OF 45 HCAPLUS COPYRIGHT 2000 ACS
AN 1975:491106 HCAPLUS
DN 83:91106
TI Effect of folic acid on the anticonvulsive action of phenobarbital and diphenylhydantoin
AU Czarnecka, Elzbieta; Zajac, Alicja; Malafiej, Eugeniusz; Draminski, Marcin
CS Dep. Pharmacol., Sch. Med., Lodz, Pol.
SO Acta Physiol. Pol. (1975), 26(2), 183-8
CODEN: APYPAY
DT Journal
LA English
GI For diagram(s), see printed CA Issue.
AB Folic acid (I) [59-30-3] (100 .mu.g/kg orally every other day for 3 weeks) administered to rats simultaneously with phenytoin (II) [57-41-0](20 mg/kg as above) markedly reduced the anticonvulsive activity of II in pentetrazole-induced seizures. In similar expts. with a single dose of I (1.5 .mu.g/animal) and II (200 mg/kg), II considerably decreased serum I level. Analogous expts. with I and phenobarbital [**50-06-6**] failed to give any **unequivocal** correlation.

L132 ANSWER 41 OF 45 HCAPLUS COPYRIGHT 2000 ACS
AN 1974:499657 HCAPLUS
DN 81:99657
TI Acute effect of some drugs on the higher nervous system activity in man. Medazepam (15 mg), oxazepam (20 mg), diazepam (10 mg). XXVIII
AU Hrbek, Jan; Komenda, S.; Siroka, A.; Macakova, J.; Vedlich, L.; Pinkava, P.
CS Med. Fac., Palacky Univ., Olomouc, Czech.
SO Acta Univ. Palacki. Olomuc., Fac. Med. (1973), 67, 115-53
CODEN: AUPMAF
DT Journal
LA English
AB Oral administration of medazepam (I) [2898-12-6] (15 mg), oxazepam (II) [**604-75-1**] (20 mg) and diazepam (III) [439-14-5] (10 mg) to human subjects did not significantly (using an anal. of variance) affect the no. of necessary repetitions, the no of correct responses and the frequencies of responses in establishment of artificial conditioned **speech** connections. However, the less strict graphic test showed a paradoxical

effect of II, which improved results 1 hr after administration and had an inhibitory effect after 2 hr. Test of the multiple range according to Duncan showed that I improved, while III impaired, response frequencies performed at 1 and 2 hrs after administration.

L132 ANSWER 42 OF 45 HCAPLUS COPYRIGHT 2000 ACS
AN 1972:280 HCAPLUS
DN 76:280
TI Acute effect of some drugs on the higher nervous activity in man. Hydrothiadene (50 mg), northiadene (50 mg), oxazepam (20 mg). XVI B. Partial analysis of the effect of the drugs on the function of the complex tactile analyzer
AU Hrbek, Jan; Komenda, S.; Macakova, J.; Siroka, A.; Paldiova, M.; Pinkava, P.
CS Med. Fac., Palacky Univ., Olomouc, Czech.
SO Acta Univ. Palacki. Olomuc., Fac. Med. (1969), 53, 199-212
CODEN: AUPMAF
DT Journal
LA English
AB The acute effects of perorally administered hydrothiaden [1886-45-9] (50 mg), northiaden [1154-09-2] (50 mg), and oxazepam (I) [**604-75-1**] (20 mg) were determined on the formation of artificial conditioned **speech** connections by means of 2 complex tactile stimuli. Criteria for the evaluation of results were the no. of repetitions necessary for mastering the given task, and the no. of correct responses and the frequency of responses in the 1st 8 repetitions. One hr after administration, only hydrothiaden produced a marked impairment in the no. of correct responses. Two hr after application of the drugs, I significantly impaired all tested characteristics, while hydrothiaden significantly impaired the frequency of responses and insignificantly impaired the no. of correct responses.
IT **604-75-1**
RL: BIOL (Biological study)
(mental activity response to, **speech** and touch in relation to)
RN 604-75-1 HCAPLUS
CN 2H-1,4-Benzodiazepin-2-one, 7-chloro-1,3-dihydro-3-hydroxy-5-phenyl- (7CI, 8CI, 9CI) (CA INDEX NAME)

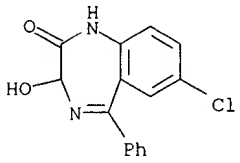


L132 ANSWER 43 OF 45 HCAPLUS COPYRIGHT 2000 ACS
AN 1972:279 HCAPLUS
DN 76:279
TI Acute effect of some drugs on the higher nervous activity in man. Hydrothiadene (50 mg), northiadene (50 mg), oxazepam (20 mg). XVI A. Partial analysis of the effect of the drugs on the function of the optic analyzer
AU Hrbek, Jan; Komenda, S.; Siroka, A.; Macakova, J.; Dudzik, J.; Paldiova, M.
CS Med. Fac., Palacky Univ., Olomouc, Czech.
SO Acta Univ. Palacki. Olomuc., Fac. Med. (1969), 53, 185-98
CODEN: AUPMAF
DT Journal
LA English
AB The acute effect of orally administered hydrothiaden (I) [1886-45-9] (50 mg), northiaden [1154-09-2] (50 mg), and oxazepam [**604-75-1**] (20 mg) was detd. on the formation of artificial conditoned **speech** connections by means of 2 optic stimuli in healthy humans. The criteria for evaluation of the results were the no. of repetitions necessary of mastering the given task, and the no. of correct responses and the

frequency of responses in the 1st 8 repetitions. Two hr after the administration of oxazepam the frequency of responses was significantly decreased. Otherwise, the formation of artificial conditioned **speech** connections mediated only by the optic analyzer was not significantly affected by the administered drug.

IT **604-75-1**
RL: BIOL (Biological study)
(mental activity response to, **speech** and vision in relation to)

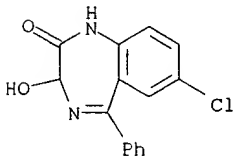
RN 604-75-1 HCAPLUS
CN 2H-1,4-Benzodiazepin-2-one, 7-chloro-1,3-dihydro-3-hydroxy-5-phenyl- (7CI, 8CI, 9CI) (CA INDEX NAME)



L132 ANSWER 44 OF 45 HCAPLUS COPYRIGHT 2000 ACS
AN 1972:278 HCAPLUS
DN 76:278
TI Acute effect of some drugs on the higher nervous activity in man. Hydrothiadene (50 mg), northiadene (50 mg), oxazepam (20 mg). XVI
AU Hrbek, Jan; Komenda, S.; Macakova, J.; Siroka, A.; Pinkava, P.; Dudzik, J.
CS Med. Fac., Palacky Univ., Olomouc, Czech.
SO Acta Univ. Palacki. Olomuc., Fac. Med. (1969), 53, 167-84
CODEN: AUPMAF
DT Journal
LA English
AB A method of artificial conditioned **speech** connections was used to study the acute effect of perorally administered hydrothiaden (I) [1886-45-9] (50 mg), northiaden [1154-09-2] (50 mg), and oxazepam (II) [**604-75-1**] (20 mg) on the higher nervous activity of healthy humans. The criteria for evaluation of the results were the no. of necessary repetitions, the no. of correct responses, and the frequency of responses during the 1st 8 repetitions. 1 Hr administration of the drugs, no significant changes were obsd. Two hr after administration of II, however, a significant impairment of the no. of necessary repetitions and the no. of correct responses was obsd. I significantly reduced the no. of correct responses, and northiaden produced a nonsignificant impairment in the no. of correct responses.

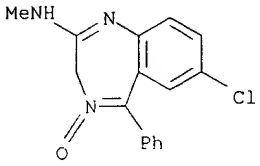
IT **604-75-1**
RL: BIOL (Biological study)
(mental activity response to, **speech** in relation to)

RN 604-75-1 HCAPLUS
CN 2H-1,4-Benzodiazepin-2-one, 7-chloro-1,3-dihydro-3-hydroxy-5-phenyl- (7CI, 8CI, 9CI) (CA INDEX NAME)



L132 ANSWER 45 OF 45 HCAPLUS COPYRIGHT 2000 ACS
AN 1968:494986 HCAPLUS
DN 69:94986
TI The acute effect of some drugs on the higher nervous activity in man. VI. Meprobamate, alimemazine, and chlordiazepoxide

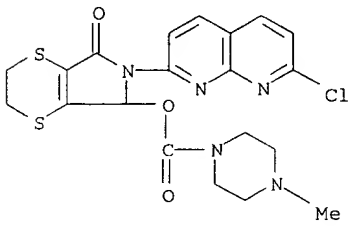
AU Hrbek, Jan; Komenda, S.; Beran, I.; Siroka, A.; Zapletalek, M.; Barborakova, E.; Kubisz, P.
CS Med. Fac., Palacky Univ., Olomouc, Czech.
SO Acta Univ. Palacki. Olomuc., Fac. Med. (1967), 47, 611-24
CODEN: AUPMAF
DT Journal
LA English
AB The method of artificial conditioned speech connections was used to study the acute effects of perorally administered meprobamate, alimenazine (Theralene), and chlordiazepoxide (Librium) on the higher nervous activity of healthy and unfatigued volunteers. The investigations were always performed before, and 1 and 2 hrs. after the administration of the drugs. A pronounced shortening of the latencies can be observed after application of Theralene in expts. carried out 1 hr. after the administration of the drug. Librium and particularly meprobamate have an inhibitory effect on the no. of necessary repetitions and the no. of correct responses. In expts. carried out 2 hrs. after the administration of Theralene, an improvement is observed in the formation, fixation, and the latencies of artificial conditioned speech connections. The inhibitory effect of Librium and particularly that of meprobamate on all the characteristics followed is persistant. Meprobamate and Librium have similar inhibitory effects on the formation of artificial conditioned speech connections.
IT **58-25-3**
RL: BIOL (Biological study)
(**speech** center response to)
RN 58-25-3 HCAPLUS
CN 3H-1,4-Benzodiazepin-2-amine, 7-chloro-N-methyl-5-phenyl-, 4-oxide (9CI) (CA INDEX NAME)



TEXT

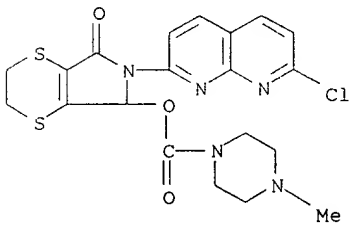
=> d bib abs hitstr l136 1-15

L136 ANSWER 1 OF 15 HCAPLUS COPYRIGHT 2000 ACS
AN 1995:527712 HCAPLUS
DN 122:282113
TI Autoradiographic distribution of [3H]suriclone binding sites in the rat brain
AU Malgouris, Christiane; Perrot, Fabienne; Dupuis, Marion; Kiosseff, Therese; Daniel, Marc; Blanchard, Jean-Charles; Doble, Adam
CS Rhone-Poulenc Rorer, Centre de Recherche de Vitry-Alfortville, Vitry-sur-Seine, Fr.
SO Drug Dev. Res. (1995), 34(4), 336-43
CODEN: DDREDK; ISSN: 0272-4391
DT Journal
LA English
AB Autoradiog. showed that the binding of [3H]suriclone to rat brain sections was displaced completely by 1 .mu.M flumazenil; satn. expts. revealed a single class of binding sites with a KD value of 1.19 nM and a Bmax of 1.05 pmol/mg protein. The pharmacol. specificity of [3H]suriclone binding was close to that of the benzodiazepine (BZ) binding site on the **GABAA receptor**. Unlike the binding of BZ agonists, [3H]suriclone binding to rat brain sections was not increased in the presence of GABA, and unlike imidazopyridines such as alpidem, suriclone was unable to discriminate between the BZ1 and BZ2 phenotype of the **GABAA receptor**. The autoradiog. distribution of [3H]suriclone binding sites in the rat brain was heterogeneous and relatively similar to that previously described for **GABAA receptors** labeled by BZs; some regions, however, such as certain cortical areas, displayed a different labeling. The highest densities were found in the frontal, occipital, parietal, and cingulate cortices (layers I, II, III, IV), in the mol. layer of the cerebellum, in the superior colliculus and in the hippocampus. Moderate binding densities appeared in numerous areas such as the inferior colliculus, the central gray, the dorsal raphe, and the hypothalamus, whereas the caudate putamen, globus pallidus, and thalamic nuclei displayed a low d. of [3H]suriclone binding sites.
IT **53813-83-5**, Suriclone
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(binding of suriclone to brain receptors)
RN 53813-83-5 HCAPLUS
CN 1-Piperazinecarboxylic acid, 4-methyl-, 6-(7-chloro-1,8-naphthyridin-2-yl)-2,3,6,7-tetrahydro-7-oxo-5H-1,4-dithiino[2,3-c]pyrrol-5-yl ester (9CI) (CA INDEX NAME)



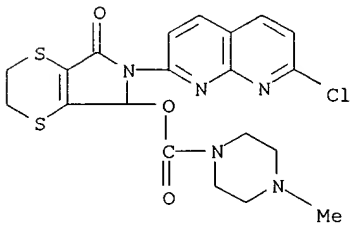
L136 ANSWER 2 OF 15 HCAPLUS COPYRIGHT 2000 ACS
AN 1995:521047 HCAPLUS
DN 122:305875
TI Characterization of novel ligands for wild-type and natural mutant diazepam-insensitive benzodiazepine receptors
AU Wong, Garry; Uusi-Oukari, Mikko; Hansen, Holger C.; Suzdak, Peter D.; Korpi, Esa R.
CS Biomedical Research Center, Alko Group Ltd, P.O. Box 350, FIN-00101, Helsinki, Finland
SO Eur. J. Pharmacol., Mol. Pharmacol. Sect. (1995), 289(2), 335-42
CODEN: EJPPET; ISSN: 0922-4106

DT Journal
LA English
AB A series of benzodiazepine receptor ligands with different chem. structures were evaluated for their affinities at diazepam-sensitive and diazepam-insensitive binding sites for [3H]Ro 15-4513 (ethyl-8-azido-5,6-dihydro-5-methyl-6-oxo-4H-imidazo-[1,5a][1,4]benzodiazep ine-3-carboxylate) in cerebellar **GABAA receptors**. Rats of Wistar strain and of alc.-sensitive (ANT) and alc.-insensitive (AT) lines were used. The ANT rats possess a single point mutation in their **GABAA receptor** .alpha.6 subunit, which makes their diazepam-insensitive sites sensitive to benzodiazepine agonists, unlike those of AT and Wistar rats. All compds. evaluated displayed high-affinity binding to diazepam-sensitive sites (Ki<50 nM). In contrast, a wider range of affinities were obsd. at diazepam-insensitive sites which depended upon the basic structure and substitutions. The 7- and 8-halogen substituted imidazobenzodiazepines and 12-halogen substituted diimidazoquinazolines displayed the highest affinities (Ki<15 nM), while intermediate to low affinities (100<Ki<4000 nM) were displayed by imidazoquinazolines, thienopyrimidines, one oxoimidazoquinoxaline, and some cyclopyrrolones. The imidazoquinoxalines evaluated displayed the lowest affinity (Ki>10000 nM). The oxoimidazoquinoxaline, 6-chloro-3-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-4,5-dihydro-5-isopropyl-4-o xo-imidazo[1,5-a]quinoxaline (NNC 14-0578) and suriclone represent the first benzodiazepine receptor full agonists to bind with relatively high affinity (Ki.apprx.100 nM) to diazepam-insensitive sites. The 5-position substituted methoxybenzyl, dimethylallyl, and 4-fluorobenzyl oxoimidazoquinoxaline analogs demonstrated a 58-336-fold higher affinity for ANT than AT diazepam-insensitive sites. Classical benzodiazepines having a 5-Ph substituent have demonstrated a similar preference for ANT sites, suggesting that all these structures bind to diazepam-insensitive sites in the same orientation. The other compds. evaluated demonstrated only a more modest selectivity (1-12-fold), indicating different structural requirements for binding to mutant ANT and wild-type AT and Wistar receptors. These results expand the range of ligands which display high affinity for diazepam-insensitive sites. Such compds. should be helpful in detg. intrinsic actions of high-affinity ligands at these sites and in assessing the contribution of these sites in enhanced sedative sensitivity of cerebellar function in the ANT rats.
IT **53813-83-5**, Suriclone
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); PRP (Properties); BIOL (Biological study); PROC (Process)
(characterization of novel ligands for wild-type and natural mutant diazepam-insensitive benzodiazepine receptors)
RN 53813-83-5 HCAPLUS
CN 1-Piperazinecarboxylic acid, 4-methyl-, 6-(7-chloro-1,8-naphthyridin-2-yl)-2,3,6,7-tetrahydro-7-oxo-5H-1,4-dithiino[2,3-c]pyrrol-5-yl ester (9CI) (CA INDEX NAME)



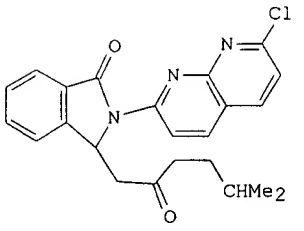
L136 ANSWER 3 OF 15 HCAPLUS COPYRIGHT 2000 ACS
AN 1995:225748 HCAPLUS
DN 122:942
TI The effect of cyclopyrrolones on **GABAA receptor** function is different from that of benzodiazepines
AU Concas, A.; Serra, M.; Santoro, G.; Maciocco, E.; Cuccheddu, T.; Biggio, G.
CS Dep. Experimental Biology, Univ. Cagliari, Cagliari, I-09123, Italy

SO Naunyn-Schmiedeberg's Arch. Pharmacol. (1994), 350(3), 294-300
CODEN: NSAPCC; ISSN: 0028-1298
DT Journal
LA English
AB The effects of the cyclopyrrolones zopiclone and suriclone on the function of the central .gamma.-amino-butyric acid type A (**GABAA**) **receptor** complex in mouse brain were evaluated both in vitro and in vivo. Added in vitro to mouse cerebral cortical membranes, these compds. potently inhibited [3H]flumazenil binding with IC50 (50% inhibitory concn.) values of 35.8 mM (zopiclone) and 1.1 nM (suriclone). Similar results were obtained with cerebellar membranes, indicating that these drugs do not discriminate between putative type I and type II benzodiazepine receptors. The interaction of cyclopyrrolones with recognition sites present at the level of the **GABA receptor** complex appears to be competitive, because zopiclone decreased the affinity to be competitive, because zopiclone decreased the affinity of the receptors for [3H]flumazenil without affecting the maximal no. of binding sites. Moreover, zopiclone and suriclone did not affect the rate of dissocn. of [3H]flumazenil from benzodiazepine receptors. The in vitro efficacy of zopiclone appeared different from that of suriclone and the benzodiazepines diazepam and flunitrazepam. Thus, zopiclone failed to affect muscimol-stimulated 36Cl- untake and only slightly inhibited t-[35S]butylbicyclophosphorothionate ([35S]TBPS) binding. In contrast, like diazepam and flunitrazepam, suriclone increased muscimol-stimulated 36Cl- uptake and markedly inhibited [35S]TBPS binding. On the other hand, suriclone, like zopiclone, did not modify [3H]muscimol binding to mouse cerebral cortical membranes. Moreover, zopiclone antagonized the redn. in [35S]TBPS binding elicited by the benzodiazepine receptor full agonist diazepam. Consistent with its low efficacy in vitro, oral administration of zopiclone (2.5 to 100 mg/kg, p.o.) in mice failed to modify [35S]TBPS binding subsequently measured in cerebral cortical membranes "ex vivo". In contrast, suriclone (10 to 20 mg/kg, p.o.), like diazepam, decreased [35S]TBPS binding measured ex vivo. Moreover, both zopiclone (50 to 100 mg/kg, p.o.) and suriclone (1 to 10 mg/kg, p.o.) abolished the increase in [35S]TBPS binding induced by isoniazid (200 mg/kg, s.c.). These results suggest that suriclone may enhance GABAergic transmission with an efficacy similar to that of diazepam. In contrast, the low efficacy of zopiclone both in vitro and in vivo suggests that this drug may act as a partial agonist at benzodiazepine receptors.
IT **53813-83-5**, Suriclone
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(effects of cyclopyrrolones on **GABAA receptor** function are different from those of benzodiazepines)
RN 53813-83-5 HCAPLUS
CN 1-Piperazinecarboxylic acid, 4-methyl-, 6-(7-chloro-1,8-naphthyridin-2-yl)-2,3,6,7-tetrahydro-7-oxo-5H-1,4-dithiino[2,3-c]pyrrol-5-yl ester (9CI) (CA INDEX NAME)

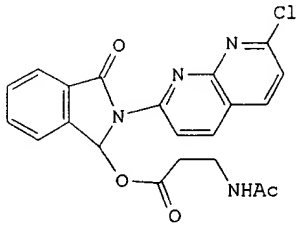


L136 ANSWER 4 OF 15 HCAPLUS COPYRIGHT 2000 ACS
AN 1994:23373 HCAPLUS
DN 120:23373
TI RP 59037 and RP 60503: Anxiolytic cyclopyrrolone derivatives with low sedative potential. Interaction with the .gamma.-aminobutyric acidA/benzodiazepine receptor complex and behavioral effects in the rodent

AU Doble, A.; Canton, T.; Dreisler, S.; Piot, O.; Boireau, A.; Stutzmann, J. M.; Bardone, M. C.; Rataud, J.; Roux, M.; et al.
CS Cent. Rech. Vitry-Alfortville, Rhone-Poulenc Rorer, Vitry-sur-Seine, 94403, Fr.
SO J. Pharmacol. Exp. Ther. (1993), 266(3), 1213-26
CODEN: JPETAB; ISSN: 0022-3565
DT Journal
LA English
GI



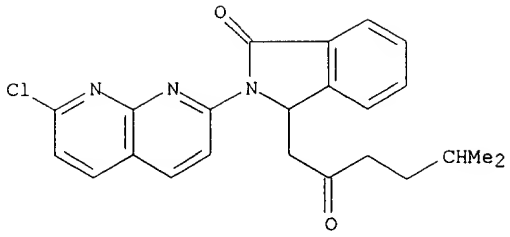
I



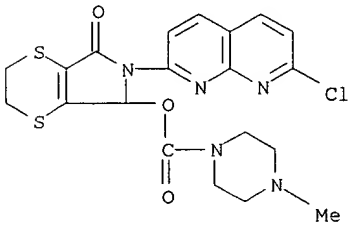
II

AB This study describes the pharmacol. properties of two novel cyclopyrrolone derivs., RP 59037 (I) and RP 60503 (II), in the rodent. These compds. possess high affinity for the benzodiazepine binding site on the .gamma.-aminobutyric acidA receptor in rat cerebrocortical membranes with Ki values of 0.98 nM (I) and 1.16 nM (II). Neither compd. discriminates between the putative benzodiazepine BZ1 and BZ2 binding site subtypes present in the rat cerebellum and hippocampus, resp. Both compds. protect mice against pentylenetetrazole-induced seizures with ID50 values of 0.21 mg.cntdot.kg-1 oral (I) and 5.96 mg.cntdot.kg-1 oral (II). The two compds. displayed a restricted anticonvulsant profile compared to diazepam and, in this respect, resembled the pyrazoloquinoline partial agonist, CGS 9896. I and II were active in two rat models predictive of anxiolytic drug action, a modified Geller-Seifter conflict paradigm (minimal effect dose, 0.33 mg.cntdot.kg-1 oral for I and 5 mg.cntdot.kg-1 oral for II and the elevated plus maze (minimal ED, 0.33 mg.cntdot.kg-1 oral for I and 5 mg.cntdot.kg-1 oral for II). Only very low activities were obsd. in tests of sedative or myorelaxant effects (EC50 > 50 mg.cntdot.kg-1 oral). It is concluded that the two cyclopyrrolones possess a dissocd. behavioral profile, displaying potent anxiolytic and anticonvulsant properties with little or no sedative or myorelaxant effects. Although both compds. appear to be partial agonists at their allosteric recognition site on the .gamma.-aminobutyric acidA receptor, II seems to be more dissocd. than I, which would be compatible with it having lower intrinsic activity. This difference is reflected in a higher receptor occupancy requirement for activity, and a smaller modulatory effect on the binding of t-[35S]butylbicyclophosphothionate.
IT **133737-32-3**, (+)-RP 59037
RL: BIOL (Biological study)
(interaction with **GABAA**/benzodiazepine **receptor**, in cerebral cortex membranes, as anxiolytic)
RN 133737-32-3 HCAPLUS
CN 1H-Isoindol-1-one, 2-(7-chloro-1,8-naphthyridin-2-yl)-2,3-dihydro-3-(5-methyl-2-oxohexyl)-, (+)- (9CI) (CA INDEX NAME)

Rotation (+).

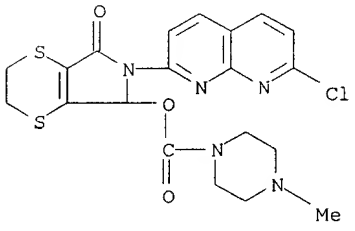


L136 ANSWER 5 OF 15 HCAPLUS COPYRIGHT 2000 ACS
AN 1993:641810 HCAPLUS
DN 119:241810
TI Expression and properties of recombinant .alpha.1.beta.2.gamma.2 and .alpha.5.beta.2.gamma.2 forms of the rat **GABAA receptor**
AU Faure-Halley, C.; Graham, D.; Arbilla, S.; Langer, S. Z.
CS Dep. Biol., Synthelabo Rech., Bagneux, F-92225, Fr.
SO Eur. J. Pharmacol., Mol. Pharmacol. Sect. (1993), 246(3), 283-7
CODEN: EJPPET; ISSN: 0922-4106
DT Journal
LA English
AB The interaction of .omega. (benzodiazepine) modulatory drugs with transiently expressed .alpha.1.beta.2.gamma.2 and .alpha.5.beta.2.gamma.2 forms of the rat **GABAA receptor** was investigated using [3H]flumazenil as a probe in in vitro radioligand binding assays. The imidazopyridines alpidem and zolpidem exhibited pronounced selectivity for the .alpha.1- compared to the .alpha.5-contg. construct, whereas .omega. (benzodiazepine) site modulatory compds. from other chem. series including diazepam, tetrazepam, zopiclone, triazolam, bretazenil and midazolam behaved as relatively non-selective drugs. In the presence of 10 .mu.M .gamma.-aminobutyric acid (GABA) the potencies of diazepam, flunitrazepam and midazolam to inhibit [3H]flumazenil binding to the .alpha.1-construct were increased 3 to 5 fold, whereas the 6,7-dimethoxy-4-ethyl-.beta.-carboline-3-carboxylate Me ester a 2.5-fold redn. in potency was obsd. Similar modulatory effects of GABA were obtained with these drugs, using the .alpha.5-construct. The authors suggest that these GABA shift detns. of [3H]flumazenil binding can be used as a rapid test to evaluate the intrinsic activities of .omega. modulatory compds.
IT **53813-83-5**, Suriclone
RL: BIOL (Biological study)
(GABAergicA .alpha.1.beta.2.gamma.2 and .alpha.5.beta.2.gamma.2 recombinant receptor subtypes binding affinity for)
RN 53813-83-5 HCAPLUS
CN 1-Piperazinecarboxylic acid, 4-methyl-, 6-(7-chloro-1,8-naphthyridin-2-yl)-2,3,6,7-tetrahydro-7-oxo-5H-1,4-dithiino[2,3-c]pyrrol-5-yl ester (9CI) (CA INDEX NAME)



L136 ANSWER 6 OF 15 HCAPLUS COPYRIGHT 2000 ACS
AN 1993:508926 HCAPLUS
DN 119:108926
TI Discriminative stimulus effects of .omega. (BZ) receptor ligands: correlation with in vivo inhibition of [3H]-flumazenil binding in

different regions of the rat central nervous system
AU Sanger, D. J.; Benavides, J.
CS Synthelabo Rech., Bagneux, F-92220, Fr.
SO Psychopharmacology (Berlin) (1993), 111(3), 315-22
CODEN: PSCHDL; ISSN: 0033-3158
DT Journal
LA English
AB Rats can be trained to discriminate benzodiazepines (BZ) from vehicle and there is considerable evidence that the stimulus effects of these drugs are mediated by activity at .omega. (BZ) modulatory sites of the **GABAA receptor** complex. A no. of recent studies, however, have indicated that differences may exist between the discriminative stimulus effects of benzodiazepines and those of certain non-benzodiazepine ligands for the .omega. (BZ) receptors (e.g. zolpidem, abecarnil). As it is known that several subtypes of .omega. (BZ) sites are found in the central nervous system, and that drugs such as zolpidem have selectivity for certain subtypes, it is possible that differential stimulus effects may be assocd. with receptor selectivity. In the present study, correlations were calcd. between the potencies of nine compds. with affinity for .omega. receptors (diazepam, lorazepam, triazolam, clonazepam, alprazolam, zopiclone, suriclone, CL 218,872 and zolpidem) to substitute for chlordiazepoxide in rats trained to discriminate a dose (5 mg/kg) of this benzodiazepine and the ability of the same compds. to inhibit the binding of [3H]flumazenil from different structures in the rat central nervous system in vivo. The correlations obtained were: cerebellum 0.46, cortex 0.39, striatum 0.78, hippocampus 0.79 and spinal cord 0.95. These different structures are known to contain different relative concns. of .omega.1 (BZ1) and .omega.2 (BZ2) sites with the spinal cord contg. the greatest (80%) and cerebellum the lowest (5%) concn. of .omega.2 (BZ2) sites. Good correlations were also obsd. between the ability of these compds. to substitute for chlordiazepoxide and their potency to inhibit (3H)-flumazenil binding in both cerebellar and spinal cord membranes in vitro indicating that the physiol. relevance of .omega. receptor subtypes cannot be deduced from in vitro studies. The present results are consistent with the possibility that the discriminative stimulus produced by chlordiazepoxide is mediated by activity of .omega.2 (BZ2) sites. No correlations were obsd. between inhibition of [3H]-flumazenil binding and response rate decreases, suggesting that the mechanism underlying this behavioral effect is different from that mediating the discriminative stimulus.
IT **53813-83-5**, Suriclone
RL: PRP (Properties)
(discriminative stimulus effects of, benzodiazepine receptors .omega.1 and .omega.2 specificity comparison for)
RN 53813-83-5 HCAPLUS
CN 1-Piperazinecarboxylic acid, 4-methyl-, 6-(7-chloro-1,8-naphthyridin-2-yl)-2,3,6,7-tetrahydro-7-oxo-5H-1,4-dithiino[2,3-c]pyrrol-5-yl ester (9CI) (CA INDEX NAME)



L136 ANSWER 7 OF 15 HCAPLUS COPYRIGHT 2000 ACS
AN 1993:400759 HCAPLUS
DN 119:759
TI Pharmacological properties and mechanism of action of the cyclopyrrolones
AU Stutzmann, J. M.; Piot, O.; Reibaud, M.; Doble, A.; Blanchard, J. C.
CS Biol. Dep., Rhone Poulenc Rorer, Vitry-sur-Seine, 94403, Fr.
SO Encephale (1992), 18(4), 393-400

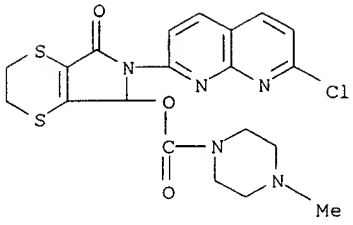
CODEN: ENCEAN; ISSN: 0013-7006
DT Journal
LA English

AB We present the pharmacol. properties of two cyclopyrrolones, P. as a hypnotic and suriclone as an anxiolytic, and examine their mechanism of action. The effects of zopiclone on the amt. of time spent at each vigilance level have been studied in freely moving rats. Zopiclone from 2.5 mg/kg i.p. extends the duration of slow wave sleep (SWS), concomitantly shortening the periods awake. This SWS inducing effect of zopiclone was more potent after 10 mg/kg i.p.; moreover, zopiclone did not depress REM sleep and no rebound of activity in wakefulness or REM sleep were obsd. the day after zopiclone treatment. In rats, at the cortical level, zopiclone increases the spectral energy in the delta band (0.5 to 4 Hz). This rise in energy appears at doses starting from 1.25 mg/kg p.o. and can also reach the fast frequencies (beta band: 12 to 16 Hz). This power spectrum is characteristic of a compd. having tranquilizing-hypnotic potential. Taken together these EEG results corroborate the clin. studies. In man, zopiclone increased SWS, decreased SWS latency and respected sleep architecture in both healthy volunteers and insomniacs. This respect of sleep structure and the relative short duration of action of zopiclone minimized the residual effects seen upon waking (drowsiness, impairment of psychomotor performance). In the Geller-Seifter test, an operant conflict procedure, the minimal ED (MED) of suriclone in reversing the conflict-induced inhibition of drinking behavior was 2.5 mg.kg-1 p.o. in rats. Depression of unpunished responding is only seen at higher doses (20 mg.kg-1 p.o.). The anxiolytic activity of suriclone has also been demonstrated using the elevated plus-maze test in mice and rats, another std. test for evaluating anxiolytic drugs which does not involve training of the animals. Suriclone increased both the amt. of time spent on the open arms and the no. of entries onto the open arms both p.o. and s.c. In mice (MED = 0.5 mg.kg-1 p.o. and 0.16 mg.kg-1 s.c.) and in rats (MED = 1.25 mg.kg-1 p.o.). Suriclone has shown a proven efficacy in patients with generalized anxiety disorders from 0.1 mg. Although it displayed considerable anxiolytic activity, suriclone appeared to have fewer central depressant effects in muscle relaxant tests, such as the inclined screen test in rats, the grasping test or the loss of righting reflex in mice. Thus in clin. practice, one can hypothesize that the use of suriclone in the treatment of anxiety may be assocd. with few side-effects including little effect on diurnal vigilance. In mice, chronic treatment with some benzodiazepines (4 times daily for 3 days), followed by 2 days withdrawal, leads to the appearance of convulsions after administration of 40 mg/kg i.p. of the partial inverse agonist FG 7142 (N-methyl-.beta. carboline carboxamide), a dose which is normally devoid of convulsant activity. In contrast, no convulsions were obsd. after chronic exposure to cyclopyrrolones, zopiclone and suriclone, even up to 400 mg/kg i.p. daily. These results were confirmed after a ten day treatment period and indicate that cyclopyrrolones do not enhance sensitivity to the partial inverse agonist FG 7142, which could suggest that these compds. do not induce phys. dependence. Anxiolytic-hypnotic drugs could modify in an allosteric manner the conformation of the **GABA receptor**-complex such that it becomes more sensitive to its neuromediator. Biochem. studies strongly suggest that cyclopyrrolones interact on an alternative binding domain to benzodiazepines or at least in a different way within the heterogeneous **GABA receptor** complex. Studies with the cyclopyrrolones confirm the importance of GABA function in the regulation of sleep and of anxiety. Zopiclone (Imovane.RTM.) and suriclone (Suri.RTM.) belong to this new chem. family and resp. possess potent hypnotic and anxiolytic activities in exptl. and clin. pharmacol.

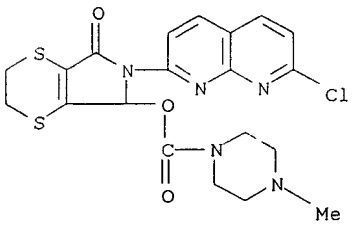
IT **53813-83-5**, Suriclone
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmacol. of, as cyclopyrrolone anxiolytic)

RN 53813-83-5 HCAPLUS

CN 1-Piperazinecarboxylic acid, 4-methyl-, 6-(7-chloro-1,8-naphthyridin-2-yl)-2,3,6,7-tetrahydro-7-oxo-5H-1,4-dithiino[2,3-c]pyrrol-5-yl ester (9CI) (CA INDEX NAME)

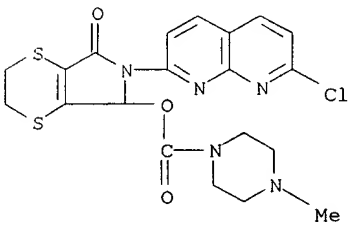


L136 ANSWER 8 OF 15 HCAPLUS COPYRIGHT 2000 ACS
AN 1992:504113 HCAPLUS
DN 117:104113
TI The pharmacology of cyclopyrrolone derivatives acting at the **GABAA** /benzodiazepine **receptor**
AU Doble, A.; Canton, T.; Piot, O.; Zundel, J. L.; Stutzmann, J. M.; Cotrel, C.; Blanchard, J. C.
CS Cent. Rech. Vitry-Alfortville, Rhone-Poulenc Rorer, Vitry-sur-Seine, 94403, Fr.
SO Adv. Biochem. Psychopharmacol. (1992), 47(GABAergic Synaptic Transm.), 407-18
CODEN: ABPYBL; ISSN: 0065-2229
DT Journal
LA English
AB Data accumulated over the last ten years have demonstrated that the cyclopyrrolones, zopiclone and suriclone, are potent allosteric modulators of **GABAA receptor** function, and possess effective hypnotic and anxiolytic advantages compared to benzodiazepines in terms of effects on vigilance and of their propensity for producing **GABAA receptor** sensitivity changes. Binding expts. have revealed that cyclopyrrolones appear to interact with a different binding domain to that of benzodiazepines. This property may underly the pharmacol. differences obsd. in vivo.
IT **53813-83-5**, Suriclone
RL: BIOL (Biological study)
(anxiolytic and hypnotic activity of, **GABAergicA** /benzodiazepine **receptors** in)
RN 53813-83-5 HCAPLUS
CN 1-Piperazinecarboxylic acid, 4-methyl-, 6-(7-chloro-1,8-naphthyridin-2-yl)-2,3,6,7-tetrahydro-7-oxo-5H-1,4-dithiino[2,3-c]pyrrol-5-yl ester (9CI) (CA INDEX NAME)



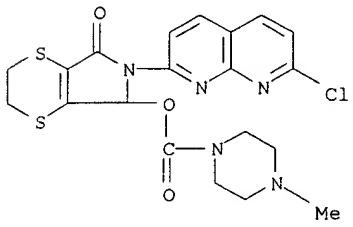
L136 ANSWER 9 OF 15 HCAPLUS COPYRIGHT 2000 ACS
AN 1991:499 HCAPLUS
DN 114:499
TI Cyclopyrrolones, unlike some benzodiazepines, do not induce physical dependence in mice
AU Piot, O.; Betschart, J.; Stutzmann, J. M.; Blanchard, J. C.
CS Cent. Rech. Vitry-Alfortville, Rhone-Poulenc Sante, Vitry sur Seine, F-94403, Fr.
SO Neurosci. Lett. (1990), 117(1-2), 140-3
CODEN: NELED5; ISSN: 0304-3940

DT Journal
LA English
AB In a model of phys. dependence in mice, treatment with cyclopyrrolones such as zopiclone and suriclone (from 4 to 400 mg/kg/day), did not modify the sensitivity of the .**gamma.-aminobutyric acid** (**GABA**) **receptor** complex to the partial inversion agonist FG 7142 following their withdrawal, whereas sensitivity changes were obsd. after treatment and withdrawal from some benzodiazepines (e.g. lorazepam, diazepam, flunitrazepam and triazolam). These data suggest that, in contrast to some benzodiazepines, zopiclone and suriclone may not produce phys. dependence.
IT **53813-83-5**, Suriclone
RL: PRP (Properties)
(phys. dependence potential of)
RN 53813-83-5 HCAPLUS
CN 1-Piperazinecarboxylic acid, 4-methyl-, 6-(7-chloro-1,8-naphthyridin-2-yl)-2,3,6,7-tetrahydro-7-oxo-5H-1,4-dithiino[2,3-c]pyrrol-5-yl ester (9CI) (CA INDEX NAME)

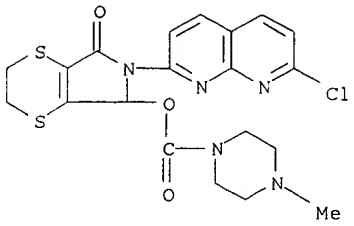


L136 ANSWER 10 OF 15 HCAPLUS COPYRIGHT 2000 ACS
AN 1990:111927 HCAPLUS
DN 112:111927
TI Interaction of suriclone with central type benzodiazepine receptors in living baboons
AU Brouillet, Emmanuel; Chavoix, Chantal; Hantraye, Philippe; Kunimoto, Masayuki; Khalili-Varasteh, Marina; Chevalier, Paul; Frydman, Armand; Gaillot, Jean; Prenant, Christian; et al.
CS Serv. Hosp. Frederic Joliot, Orsay, 91406, Fr.
SO Eur. J. Pharmacol. (1990), 175(1), 49-55
CODEN: EJPHAZ; ISSN: 0014-2999
DT Journal
LA English
AB The interaction of suriclone and two of its main metabolites with central type benzodiazepine receptors, which had been labeled in vivo with the radioligand [14C]RO 15-1788, was investigated in baboons. The concn. of radioligand bound to the receptors, as measured in brain transverse sections by positron emission tomog., decreased rapidly after the i.v. administration of suriclone at doses known to induce pharmacol. effects. Te rate and extent to which [11C]RO 15-1788 binding was displaced increased with increasing doses of suriclone. The half-ID was 0.08 mg/kg. The rapid inhibitory effect of suriclone on the in vivo binding of [14C]RO 15-1788 in the brain seems to reflect its ability to act at the **GABA**-benzodiazepine **receptor** complex, at or near the benzodiazepine binding site, to induce its pharmacol. activity. The i.v. injection of the demethylated metabolite of suriclone, RP 35,489, caused only a slight displacement of [14C]RO 15-1788 binding even at 2 mg/kg. Thus, suriclone appears to be more potent than RP 35,489 is displacing the benzodiazepine antagonist in vivo. The sulfoxide metabolite, RP 46,166, did not change the kinetics of [11C]RO 15-1788 binding in the brain. The slight effects produced by high doses of RP 35,489 and RP 46,166 on [14C]Ro 15-1788 binding in the brain suggest that these metabolites are probably not responsible for the biol. activity of suriclone mediated by benzodiazepine receptors.
IT **53813-83-5**, Suriclone
RL: PROC (Process)
(binding of, to benzodiazepine receptors of brain)

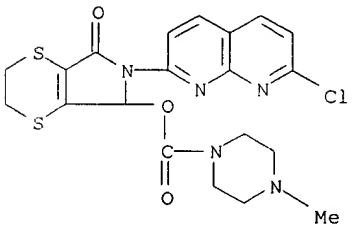
RN 53813-83-5 HCAPLUS
CN 1-Piperazinecarboxylic acid, 4-methyl-, 6-(7-chloro-1,8-naphthyridin-2-yl)-2,3,6,7-tetrahydro-7-oxo-5H-1,4-dithiino[2,3-c]pyrrol-5-yl ester (9CI) (CA INDEX NAME)



L136 ANSWER 11 OF 15 HCAPLUS COPYRIGHT 2000 ACS
AN 1988:604822 HCAPLUS
DN 109:204822
TI In vivo determination of the profile of benzodiazepine ligands by comparing the inhibition of 3H-Ro 15-1788 binding to the modulation of cGMP levels in mouse cerebellum
AU Boireau, A.; Martel, M.; Farges, G.; Dubedat, P.; Laduron, P. M.; Blanchard, J. C.
CS Cent. Rech. Vitry, Rhone-Poulenc Sante, Vitry-sur-Seine, 94403, Fr.
SO Biochem. Pharmacol. (1988), 37(19), 3765-9
CODEN: BCPCA6; ISSN: 0006-2952
DT Journal
LA English
AB The in vivo effects of various benzodiazepine (BZD) ligands belonging to different chem. families were studied comparatively in mouse cerebellum by using displacement of [3H]Ro 15-1788 binding and cGMP content as biochem. tools. It was possible to differentiate 4 classes of compds. with regard to these biochem. parameters. The 1st class of compds. such as diazepam and suriclone induced a net effect on in vivo [3H]Ro 15-1788 binding and a dose-dependent decrease of cGMP levels. A 2nd class of drugs such as ZK 91296 and CGS 9896 showed in vivo activities in displacement studies but relatively small or moderate activities on cGMP levels. A 3rd class was represented by Ro 15-1788 itself which prevented dose-dependently the in vivo [3H]Ro 15-1788 binding but was devoid of effect on cGMP levels. Finally, a 4th class of compds. (CGS 8216, FG 7142, .beta.-CCM, and DMCM) showed in vivo displacement of [3H]Ro 15-1788 with a concomitant increase of cGMP levels. The 1st class of compds. represents full agonists, the 2nd class, partial agonists, the 3rd class, the antagonist Ro-15-1788 itself, and the 4th class corresponds to inverse agonists. Thus, [3H]Ro 15-1788 binding and cGMP levels can be used to differentiate in vivo BZD ligands acting on the BZD **receptor/GABA** **receptor**/chloride ionophore complex.
IT **53813-83-5**, Suriclone
RL: BIOL (Biological study)
(as benzodiazepine receptor agonist, Ro 15-1788 displacement and cerebellar cGMP response in relation to)
RN 53813-83-5 HCAPLUS
CN 1-Piperazinecarboxylic acid, 4-methyl-, 6-(7-chloro-1,8-naphthyridin-2-yl)-2,3,6,7-tetrahydro-7-oxo-5H-1,4-dithiino[2,3-c]pyrrol-5-yl ester (9CI) (CA INDEX NAME)

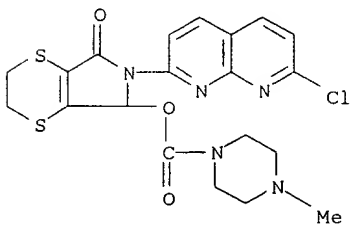


L136 ANSWER 12 OF 15 HCAPLUS COPYRIGHT 2000 ACS
AN 1987:432608 HCAPLUS
DN 107:32608
TI Stereochemical features controlling binding and intrinsic activity properties of benzodiazepine-receptor ligands
AU Borea, Pier Andrea; Gilli, Gastone; Bertolasi, Valerio; Ferretti, Valeria
CS Ist. Farmacol., Univ. Ferrara, Ferrara, 44100, Italy
SO Mol. Pharmacol. (1987), 31(4), 334-44
CODEN: MOPMA3; ISSN: 0026-895X
DT Journal
LA English
AB Benzodiazepine-receptor ligands belong to several different chem. classes. All of them bind to the receptor but display a variety of biol. effects ranging from agonist to inverse agonist to antagonist. The properties of the most representative compds. for each class are briefly reviewed as concerns their **receptor** binding affinities, **.gamma.-aminobutyric acid** ratios, photoaffinity labeling ratios, and pharmacol. properties. Their geometries, as obtained by X-ray crystallog., are discussed and missing crystal and mol. structures of 2 of them (zopiclone and CL 218-872) are reported. Binding and intrinsic activity properties of series of benzodiazepines and .beta.-carbolines are extensively analyzed and correlated with their mol. structures. A general stereochem. model accounting for both binding abilities and kinds of biochem. and pharmacol. activities for all benzodiazepine-receptor ligands is proposed. This is based on the assumption of a rather diffuse and substantially planar recognition site where the main drug-receptor interactions are mediated by the drug carbonylic or iminic groups via hydrogen bonding and the obsd. differences in pharmacol. profiles are accounted for by the different localization of the different ligands inside this unique binding site.
IT **53813-83-5**, Suriclone
RL: BIOL (Biological study)
(receptor binding by, structure in relation to)
RN 53813-83-5 HCAPLUS
CN 1-Piperazinecarboxylic acid, 4-methyl-, 6-(7-chloro-1,8-naphthyridin-2-yl)-2,3,6,7-tetrahydro-7-oxo-5H-1,4-dithiino[2,3-c]pyrrol-5-yl ester (9CI) (CA INDEX NAME)



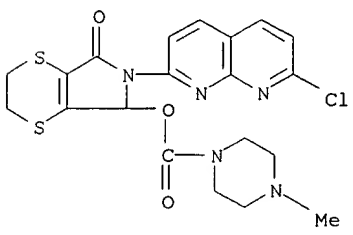
L136 ANSWER 13 OF 15 HCAPLUS COPYRIGHT 2000 ACS
AN 1986:546045 HCAPLUS
DN 105:146045
TI Pharmacological studies on stress-induced increase in frontal cortical

dopamine metabolism in the rat
AU Claustre, Yves; Rivy, Jean Paul; Dennis, Trevor; Scatton, Bernard
CS Lab. Etud. Rech. Synth., Bagneux, 92220, Fr.
SO J. Pharmacol. Exp. Ther. (1986), 238(2), 693-700
CODEN: JPETAB; ISSN: 0022-3565
DT Journal
LA English
AB The effects of a variety of minor tranquilizers and of benzodiazepine inverse agonists on the stress-induced increase in frontal cortical dopamine [51-61-6] metab. were studied in the rat. Elec. footshock stress increased 3,4-dihydroxyphenylacetic acid (DOPAC) [102-32-9] levels in the frontal (but not parietal) cortex and in the nucleus accumbens but not in the striatum or ventral tegmental area. Similar stress-induced alterations of frontal cortical DOPAC levels were obsd. after DSP4-induced noradrenergic denervation or after adrenalectomy. Other types of stress, e.g., conditioned fear (exposure to an environment paired previously with footshock) or swim stress also provoked an elevation of DOPAC levels in the prefrontal cortex. When administered systemically, the anxiolytic agents meprobamate [57-53-4], CL 218872 [66548-69-4], CGS 9896 [77779-36-3], and suriclone [**53813-83-5**] and the hypnotic/anxiolytic drugs zolpidem [82626-48-0] and zopiclone [43200-80-2] all prevented the elec. footshock stress-induced augmentation of cortical DOPAC levels, whereas the **GABA receptor** agonists progabide [62666-20-0], muscimol [2763-96-4] and depamide [2430-27-5] or the sedative .alpha.1-adrenoceptor antagonist prazosin [19216-56-9] were ineffective. The preventive effect of diazepam [439-14-5] and zolpidem on the stress-induced biochem. response was antagonized by the benzodiazepine antagonist CGS 8216 [77779-60-3] but not by the **GABA receptor** antagonist (.+-.)-bicuculline [56083-00-2]. In nonstressed rats, systemic administration of the anxiogenic benzodiazepine inverse agonists .beta.-CCM (Me .beta.-carboline-3-carboxylate) [69954-48-9] and .beta.-CCE (Et .beta.-carboline-3-carboxylate) [74214-62-3], but not of the benzodiazepine antagonists Ro 15-1788 [78755-81-4] or CGS 8216, caused an increase in frontal cortical DOPAC similar to that provoked by stress and which was antagonized by zolpidem. Finally, local injection of zolpidem (up to 10 .mu.g) into the prefrontal cortex or into the ventral tegmental area failed to prevent the footshock stress-induced increase in frontal cortical DOPAC levels. It is concluded that (with the exception of meprobamate) minor tranquilizers antagonize stress-induced increase in frontal cortical dopamine metab. via interaction with benzodiazepine receptors, this effect likely being related to the anxiolytic properties of these drugs. The effect of minor tranquilizers does not appear to be related to a direct action on dopaminergic neurons. The fact that benzodiazepine inverse agonists activate frontal cortical dopamine metab. as does stress adds further support to the view that the mesoprefrontal dopaminergic system is involved in emotional behavior.
IT **53813-83-5**
RL: BIOL (Biological study)
(stress-induced frontal cortex dopamine metab. increase prevention by)
RN 53813-83-5 HCAPLUS
CN 1-Piperazinecarboxylic acid, 4-methyl-, 6-(7-chloro-1,8-naphthyridin-2-yl)-2,3,6,7-tetrahydro-7-oxo-5H-1,4-dithiino[2,3-c]pyrrol-5-yl ester (9CI) (CA INDEX NAME)

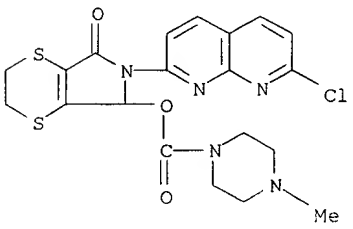


L136 ANSWER 14 OF 15 HCAPLUS COPYRIGHT 2000 ACS
SEARCHED BY SUSAN HANLEY 305-4053

AN 1985:55570 HCAPLUS
DN 102:55570
TI Anxiolytic cyclopyrrolone drugs allosterically modulate the binding of [35S]t-butylbicyclophosphorothionate to the benzodiazepine/.**gamma**.-**aminobutyric acid**-A **receptor**/chloride anionophore complex
AU Trifiletti, Rosario R.; Snowman, Adele M.; Snyder, Solomon H.
CS Sch. Med., Johns Hopkins Univ., Baltimore, MD, 21205, USA
SO Mol. Pharmacol. (1984), 26(3), 470-6
CODEN: MOPMA3; ISSN: 0026-895X
DT Journal
LA English
AB The influence of a no. of anxiolytic cyclopyrrolone drugs, which include zopiclone [43200-80-2] and suriclone [**53813-83-5**], on the binding of 35S-labeled t-butylbicyclophosphorothionate (TBPS) [70636-86-1] to benzodiazepine/.**gamma**.-**aminobutyric acid**-A **receptor**/chloride anionophore complexes has been characterized in rat brain. Suriclone and its metabolites RP35,489 [94342-72-0] and RP46,166 [94342-73-1] are the most potent (IC50 .apprx. 3nM) inhibitors of [35S]TBPS binding thus far described, about an order of magnitude more potent than TBPS itself. The pattern of inhibition of [35S]TBPS binding by suriclone is distinctive; at .apprx.10 nM there is approx. 50% inhibition of [35S]TBPS binding and inhibition "plateaus" at this level until suriclone concns. exceed 1 .mu.M. RP35,489 and RP46,166 display patterns of inhibition similar to suriclone. In satn. studies of [35S]TBPS binding, suriclone reduces the Bmax of [35S]TBPS-binding sites, with little or no effect on KD. Muscimol [2763-96-4] also displays a noncompetitive pattern of inhibition of [35S]TBPS binding, whereas inhibition by picrotoxinin [17617-45-7] appears competitive. [35S]TBPS dissocn. is multiphasic and similar whether initiated by 10 .mu.M TBPS or 10 .mu.M picrotoxinin. By contrast, dissocn. of [35S]TBPS is much faster (and nearly monophasic) when initiated by 10 .mu.M TBPS/100 nM suriclone, 10 .mu.M TBPS/1 .mu.M muscimol, or 10 .mu.M TBPS/1 mM pentobarbital [76-74-4]. Apparently, suriclone influences [35S]TBPS binding allosterically at sites distinct from the TBPS/picrotoxinin recognition site. Inhibition of [35S]TBPS binding by suriclone varies regionally with a "plateau" at .apprx.20% inhibition in the cerebellum, .apprx.50% in the cerebral cortex, hippocampus and brain stem, and .apprx.65% in the striatum and midbrain; by contrast, inhibition of [35S]TBPS by picrotoxinin, muscimol, and pentobarbital shows little regional variation. The inhibition of [35S]TBPS binding by suriclone is reversed by bicuculline [485-49-4] [ED50 .apprx.1 .mu.M] in several brain regions examd. Bicuculline alone has little or no influence on [35S]TBPS binding in the cerebral cortex, hippocampus, and cerebellum, but produces a dose-dependent enhancement of [35S]TBPS binding in the striatum, midbrain, and hypothalamus. Regional differences in the effects of suriclone and bicuculline on [35S]TBPS recognition sites suggest possible heterogeneity in the coupling of cyclopyrrolone and bicuculline recognition sites to [35S]TBPS recognition sites in rat brain.
IT **53813-83-5**
RL: BIOL (Biological study)
(butylbicyclophosphorothionate binding to brain benzodiazepine-**GABA receptor** complex response to)
RN 53813-83-5 HCAPLUS
CN 1-Piperazinecarboxylic acid, 4-methyl-, 6-(7-chloro-1,8-naphthyridin-2-yl)-2,3,6,7-tetrahydro-7-oxo-5H-1,4-dithiino[2,3-c]pyrrol-5-yl ester (9CI) (CA INDEX NAME)



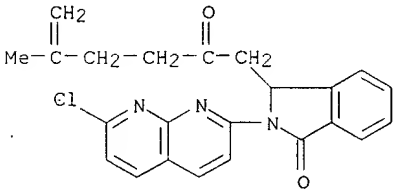
L136 ANSWER 15 OF 15 HCAPLUS COPYRIGHT 2000 ACS
AN 1984:583945 HCAPLUS
DN 101:183945
TI Suriclone, a new anxiolytic of the cyclopyrrolone family: evidence for possible interference with GABAergic systems
AU Boireau, Alain; Stutzmann, Jean Marie; Garret, Claude; Julou, Louis; Blanchard, Jean Charles
CS Cent. Rech. Vitry, Rhone-Poulenc Sante, Vitry sur Seine, 94407, Fr.
SO Eur. J. Pharmacol. (1984), 104(1-2), 139-44
CODEN: EJPHAZ; ISSN: 0014-2999
DT Journal
LA English
AB The action of suriclone (R.P. 31,264) [**53813-83-5**] was examd. using biochem. and electrophysiol. models capable of revealing central GABAergic activity. Suriclone, which does not act directly on the **GABA** [56-12-2] **receptor** (muscimol binding assay, markedly reduced the increase of striatal homovanilic acid [306-08-1] induced in the rat by a neuroleptic and decreased the cerebellar vermis cGMP [7665-99-8] content. Moreover, in the cat, suriclone enhanced dorsal root potential amplitude which reflects an increase of the presynaptic inhibition. In view of these results, a central GABAergic mechanism of action may be proposed for suriclone.
IT **53813-83-5**
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(GABAergic system of brain response to)
RN 53813-83-5 HCAPLUS
CN 1-Piperazinecarboxylic acid, 4-methyl-, 6-(7-chloro-1,8-naphthyridin-2-yl)-2,3,6,7-tetrahydro-7-oxo-5H-1,4-dithiino[2,3-c]pyrrol-5-yl ester (9CI) (CA INDEX NAME)



=> d bib abs hitstr 143 1

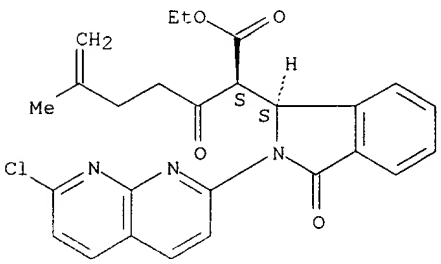
L43 ANSWER 1 OF 3 USPATFULL
AN 97:93774 USPATFULL
TI Isoindolinone derivative, preparation thereof and pharmaceutical compositions containing same
IN Barreau, Michel, Montgeron, France
Cheve, Michel, Soisy Sur Seine, France
Dubroeucq, Marie-Christine, Enghein les Bains, France
Dutruc-Rosset, Gilles, Paris, France
Manfre, Franco, Limeil-Brevannes, France
PA Rhone-Poulec Rorer S.A., Antony Cedex, France (non-U.S. corporation)
PI US 5676831 19971014
AI US 1996-712282 19960911 (8)
RLI Division of Ser. No. US 1995-476749, filed on 7 Jun 1995, now patented, Pat. No. US 5599936 which is a division of Ser. No. US 1994-286294, filed on 5 Aug 1994, now patented, Pat. No. US 5494915
PRAI FR 1992-1382 19920207
DT Utility
EXNAM Primary Examiner: Therkorn, Ernest G.
LREP Parker, III, Raymond S.; Savitzky, Martin F.
CLMN Number of Claims: 4
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 470
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to a new isoindolinone derivative of formula: ##STR1## in racemic form or in the form of its enantiomers, as well as its salts, its preparation and the pharmaceutical compositions which contain it.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **153046-20-9P 153046-22-1P 153046-25-4P**
153046-26-5P
(prepn. and reaction of, in prepn. of benzodiazepine receptor ligand)
RN 153046-20-9 USPATFULL
CN 1H-Isoindol-1-one, 2-(7-chloro-1,8-naphthyridin-2-yl)-2,3-dihydro-3-(5-methyl-2-oxo-5-hexenyl)- (9CI) (CA INDEX NAME)



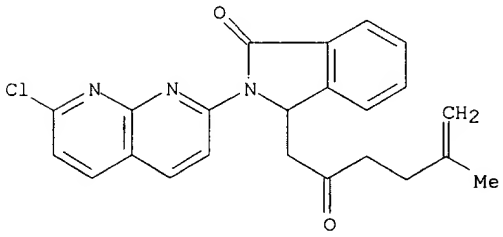
RN 153046-22-1 USPATFULL
CN 1H-Isoindole-1-acetic acid, 2-(7-chloro-1,8-naphthyridin-2-yl)-2,3-dihydro-.alpha.-(4-methyl-1-oxo-4-pentenyl)-3-oxo-, ethyl ester, (R*,R*)- (9CI) (CA INDEX NAME)

Relative stereochemistry.



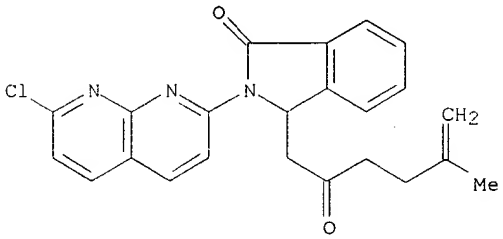
RN 153046-25-4 USPATFULL
CN 1H-Isoindol-1-one, 2-(7-chloro-1,8-naphthyridin-2-yl)-2,3-dihydro-3-(5-methyl-2-oxo-5-hexenyl)-, (+)- (9CI) (CA INDEX NAME)

Rotation (+).



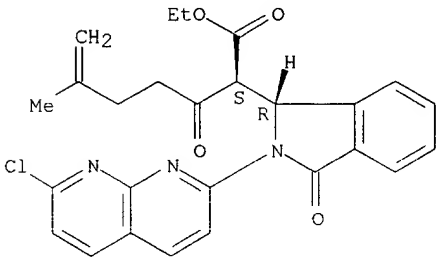
RN 153046-26-5 USPATFULL
CN 1H-Isoindol-1-one, 2-(7-chloro-1,8-naphthyridin-2-yl)-2,3-dihydro-3-(5-methyl-2-oxo-5-hexenyl)-, (-)- (9CI) (CA INDEX NAME)

Rotation (-).

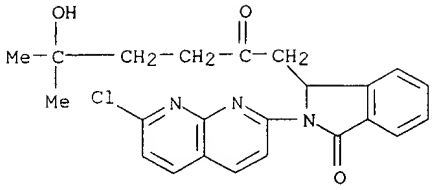


IT **153046-28-7P**
(prepn. of)
RN 153046-28-7 USPATFULL
CN 1H-Isoindole-1-acetic acid, 2-(7-chloro-1,8-naphthyridin-2-yl)-2,3-dihydro-.alpha.-(4-methyl-1-oxo-4-pentenyl)-3-oxo-, ethyl ester, (R*,S*)- (9CI) (CA INDEX NAME)

Relative stereochemistry.

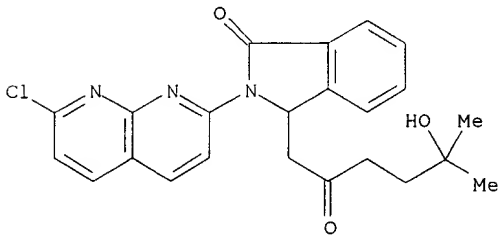


IT **153046-19-6P 153046-23-2P 153046-24-3P**
(prepn. of, as benzodiazepine receptor ligand)
RN 153046-19-6 USPATFULL
CN 1H-Isoindol-1-one, 2-(7-chloro-1,8-naphthyridin-2-yl)-2,3-dihydro-3-(5-hydroxy-5-methyl-2-oxohexyl)- (9CI) (CA INDEX NAME)



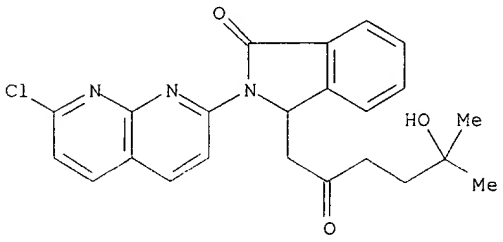
RN 153046-23-2 USPATFULL
CN 1H-Isoindol-1-one, 2-(7-chloro-1,8-naphthyridin-2-yl)-2,3-dihydro-3-(5-hydroxy-5-methyl-2-oxohexyl)-, (-)- (9CI) (CA INDEX NAME)

Rotation (-).



RN 153046-24-3 USPATFULL
CN 1H-Isoindol-1-one, 2-(7-chloro-1,8-naphthyridin-2-yl)-2,3-dihydro-3-(5-hydroxy-5-methyl-2-oxohexyl)-, (+)- (9CI) (CA INDEX NAME)

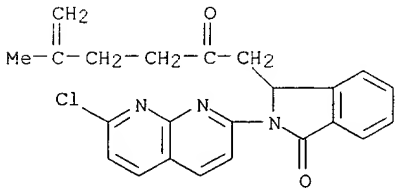
Rotation (+).



=> d bib abs hitstr l43 2

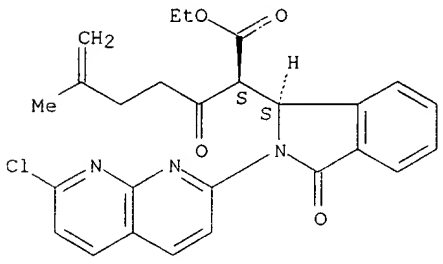
L43 ANSWER 2 OF 3 USPATFULL
AN 97:10152 USPATFULL
TI Isoindolinone derivative, preparation thereof and pharmaceutical compositions containing same
IN Barreau, Michel, Montgeron, France
Cheve, Michel, Soisy Sur Seine, France
Dubroeucq, Marie-Christine, Enghein les Bains, France
Dutruc-Rosset, Gilles, Paris, France
Manfre, Franco, Limeil-Brevannes, France
PA Rhone-Poulenc Rorer S.A., Antony Cedex, France (non-U.S. corporation)
PI US 5599936 19970204
AI US 1995-476749 19950607 (8)
RLI Division of Ser. No. US 1994-286294, filed on 5 Aug 1994, now patented, Pat. No. US 5494915
PRAI FR 1992-1382 19920207
DT Utility
EXNAM Primary Examiner: Ivy, C. Warren; Assistant Examiner: Huang, Evelyn
LREP Parker, III, Raymond S.; Savitzky, Martin F.; Nicholson, James A.
CLMN Number of Claims: 6
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 490
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to a new isoindolinone derivative of formula: ##STR1## in racemic form or in the form of its enantiomers, as well as its salts, its preparation and the pharmaceutical compositions which contain it.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **153046-20-9P 153046-22-1P 153046-25-4P**
153046-26-5P
(prepn. and reaction of, in prepn. of benzodiazepine receptor ligand)
RN 153046-20-9 USPATFULL
CN 1H-Isoindol-1-one, 2-(7-chloro-1,8-naphthyridin-2-yl)-2,3-dihydro-3-(5-methyl-2-oxo-5-hexenyl)- (9CI) (CA INDEX NAME)



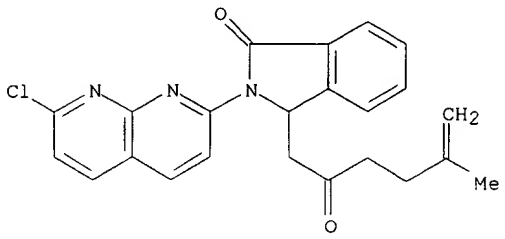
RN 153046-22-1 USPATFULL
CN 1H-Isoindole-1-acetic acid, 2-(7-chloro-1,8-naphthyridin-2-yl)-2,3-dihydro-.alpha.-(4-methyl-1-oxo-4-pentenyl)-3-oxo-, ethyl ester, (R*,R*)- (9CI) (CA INDEX NAME)

Relative stereochemistry.



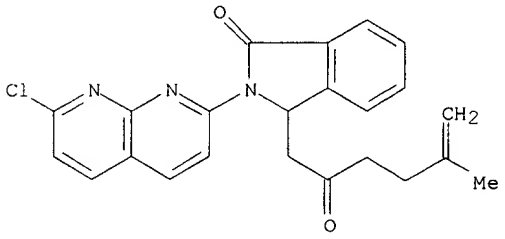
RN 153046-25-4 USPATFULL
CN 1H-Isoindol-1-one, 2-(7-chloro-1,8-naphthyridin-2-yl)-2,3-dihydro-3-(5-methyl-2-oxo-5-hexenyl)-, (+)- (9CI) (CA INDEX NAME)

Rotation (+).



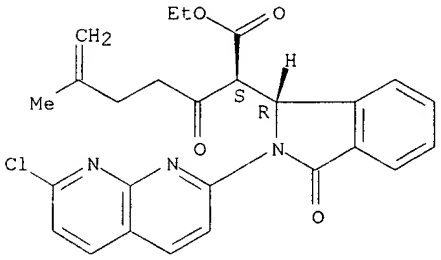
RN 153046-26-5 USPATFULL
CN 1H-Isoindol-1-one, 2-(7-chloro-1,8-naphthyridin-2-yl)-2,3-dihydro-3-(5-methyl-2-oxo-5-hexenyl)-, (-)- (9CI) (CA INDEX NAME)

Rotation (-).

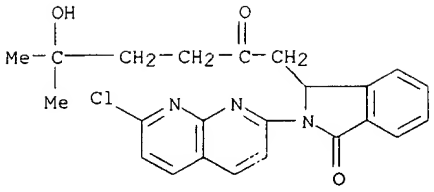


IT **153046-28-7P**
(prepn. of)
RN 153046-28-7 USPATFULL
CN 1H-Isoindole-1-acetic acid, 2-(7-chloro-1,8-naphthyridin-2-yl)-2,3-dihydro-.alpha.-(4-methyl-1-oxo-4-pentenyl)-3-oxo-, ethyl ester, (R*,S*)- (9CI) (CA INDEX NAME)

Relative stereochemistry.

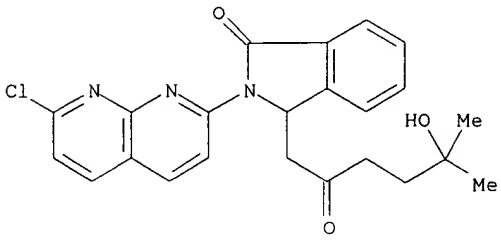


IT **153046-19-6P 153046-23-2P 153046-24-3P**
(prepn. of, as benzodiazepine receptor ligand)
RN 153046-19-6 USPATFULL
CN 1H-Isoindol-1-one, 2-(7-chloro-1,8-naphthyridin-2-yl)-2,3-dihydro-3-(5-hydroxy-5-methyl-2-oxohexyl)- (9CI) (CA INDEX NAME)



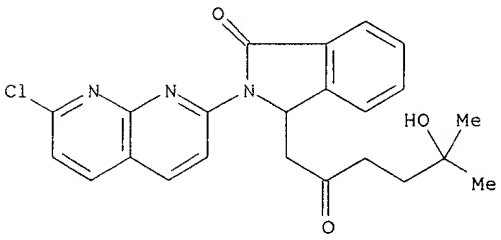
RN 153046-23-2 USPATFULL
CN 1H-Isoindol-1-one, 2-(7-chloro-1,8-naphthyridin-2-yl)-2,3-dihydro-3-(5-hydroxy-5-methyl-2-oxohexyl)-, (-)- (9CI) (CA INDEX NAME)

Rotation (-).



RN 153046-24-3 USPATFULL
CN 1H-Isoindol-1-one, 2-(7-chloro-1,8-naphthyridin-2-yl)-2,3-dihydro-3-(5-hydroxy-5-methyl-2-oxohexyl)-, (+)- (9CI) (CA INDEX NAME)

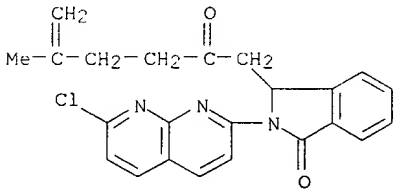
Rotation (+).



=> d bib abs hitstr l43 3

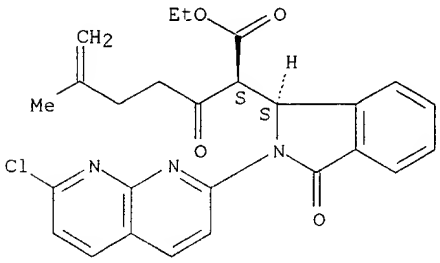
L43 ANSWER 3 OF 3 USPATFULL
AN 96:16992 USPATFULL
TI Isoindolinone derivative, preparation thereof, and pharmaceutical compositions containing same
IN Barreau, Michel, Montgeron, France
Cheve, Michel, Soisy Sur Seine, France
Dubroeucq, Marie-Christine, Enghein les Bains, France
Dutruc-Rosset, Gilles, Paris, France
Manfre, Franco, Limeil-Brevannes, France
PA Rhone-Poulenc Rorer S.A., Antony Cedex, France (non-U.S. corporation)
PI US 5494915 19960227
AI US 1994-286294 19940805 (8)
PRAI FR 1992-1382 19920207
DT Utility
EXNAM Primary Examiner: Ivy, C. Warren; Assistant Examiner: Huang, Evelyn
LREP Parker, II, Raymond S.; Savitzky, Martin F.; Nicholson, James A.
CLMN Number of Claims: 2
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 452
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to a new isoindolinone derivative of formula: ##STR1## in racemic form or in the form of its enantiomers, as well as its salts, its preparation and the pharmaceutical compositions which contain it.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **153046-20-9P 153046-22-1P 153046-25-4P 153046-26-5P**
(prepn. and reaction of, in prepn. of benzodiazepine receptor ligand)
RN 153046-20-9 USPATFULL
CN 1H-Isoindol-1-one, 2-(7-chloro-1,8-naphthyridin-2-yl)-2,3-dihydro-3-(5-methyl-2-oxo-5-hexenyl)- (9CI) (CA INDEX NAME)



RN 153046-22-1 USPATFULL
CN 1H-Isoindole-1-acetic acid, 2-(7-chloro-1,8-naphthyridin-2-yl)-2,3-dihydro-.alpha.-(4-methyl-1-oxo-4-pentenyl)-3-oxo-, ethyl ester, (R*,R*)- (9CI) (CA INDEX NAME)

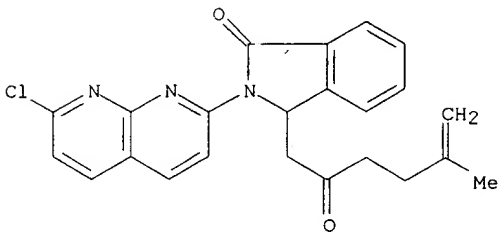
Relative stereochemistry.



RN 153046-25-4 USPATFULL

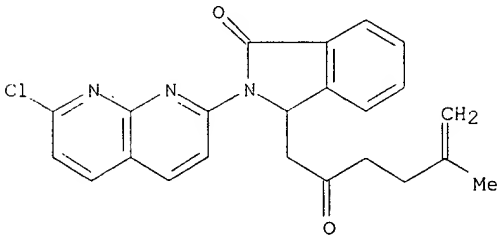
CN 1H-Isoindol-1-one, 2-(7-chloro-1,8-naphthyridin-2-yl)-2,3-dihydro-3-(5-methyl-2-oxo-5-hexenyl)-, (+)- (9CI) (CA INDEX NAME)

Rotation (+).



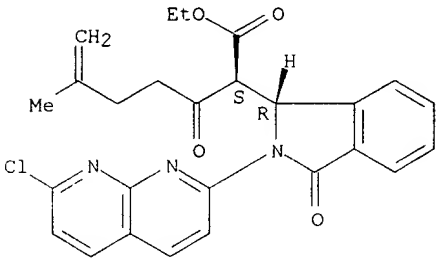
RN 153046-26-5 USPATFULL
CN 1H-Isoindol-1-one, 2-(7-chloro-1,8-naphthyridin-2-yl)-2,3-dihydro-3-(5-methyl-2-oxo-5-hexenyl)-, (-)- (9CI) (CA INDEX NAME)

Rotation (-).

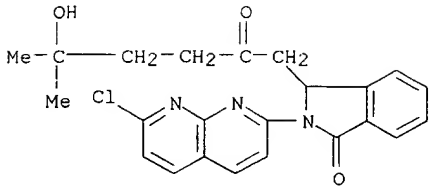


IT **153046-28-7P**
(prepn. of)
RN 153046-28-7 USPATFULL
CN 1H-Isoindole-1-acetic acid, 2-(7-chloro-1,8-naphthyridin-2-yl)-2,3-dihydro-.alpha.-(4-methyl-1-oxo-4-pentenyl)-3-oxo-, ethyl ester, (R*,S*)- (9CI) (CA INDEX NAME)

Relative stereochemistry.

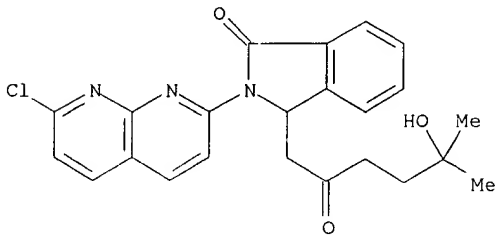


IT **153046-19-6P 153046-23-2P 153046-24-3P**
(prepn. of, as benzodiazepine receptor ligand)
RN 153046-19-6 USPATFULL
CN 1H-Isoindol-1-one, 2-(7-chloro-1,8-naphthyridin-2-yl)-2,3-dihydro-3-(5-hydroxy-5-methyl-2-oxohexyl)- (9CI) (CA INDEX NAME)



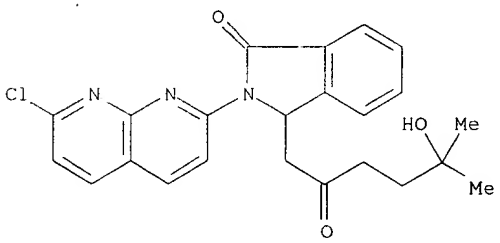
RN 153046-23-2 USPATFULL
CN 1H-Isoindol-1-one, 2-(7-chloro-1,8-naphthyridin-2-yl)-2,3-dihydro-3-(5-hydroxy-5-methyl-2-oxohexyl)-, (-)- (9CI) (CA INDEX NAME)

Rotation (-).



RN 153046-24-3 USPATFULL
CN 1H-Isoindol-1-one, 2-(7-chloro-1,8-naphthyridin-2-yl)-2,3-dihydro-3-(5-hydroxy-5-methyl-2-oxohexyl)-, (+)- (9CI) (CA INDEX NAME)

Rotation (+).



=> d kwic 3

L43 ANSWER 3 OF 3 USPATFULL
DETD Generally **speaking**, the doctor will determine the dosage which he considers to be the most suitable, depending on the age, the weight.
. .
IT **153046-20-9P 153046-22-1P 153046-25-4P**
153046-26-5P
(prepn. and reaction of, in prepn. of benzodiazepine receptor ligand)
IT **153046-28-7P**
(prepn. of)
IT **153046-19-6P 153046-23-2P 153046-24-3P**
(prepn. of, as benzodiazepine receptor ligand)

TEXT SEARCH

Claim 2

=> d his

```
     (FILE 'HOME' ENTERED AT 09:28:40 ON 06 DEC 2000)

     FILE 'HCAPLUS' ENTERED AT 09:28:47 ON 06 DEC 2000
L1          1745 S MURPHY J?/AU
                 E JORGENSON/AU
L2            15 S E28-31
                 E D ORLANDO/AU
L3             3 S E5-E6
L4             0 S L1 AND L2-3
L5          1763 S L1-3
L6         28058 S GABA
L7            12 S L5 AND L6
L8         86314 S ?INDOL?
L9             0 S ?PAGOCLON?
L10           62 S ?SURICLON?
L11            1 S L7 AND (L8 OR L10)
L12          104 S STUTTER?
L13            0 S L7 AND L12
L14            0 S L5 AND L12
L15         2894 S ?NAPHTHYRIDIN?
L16            0 S L7 AND L15
L17       231224 S ?PYRIDIN?
L18            0 S L7 AND L17
L19           12 S L17 AND L5
L20            0 S L5 AND L10
L21            0 S L5 AND L15
L22           17 S L5 AND L8
L23        15095 S ?AMINOBUTYRIC?
L24            1 S (L23 OR L6) AND (L19 OR L22)
L25            1 S L11 OR L24
                 SELECT RN L25 1

     FILE 'REGISTRY' ENTERED AT 09:41:43 ON 06 DEC 2000
L26            9 S E1-9

     FILE 'HCAPLUS' ENTERED AT 09:42:18 ON 06 DEC 2000
L27            1 S L25 AND L26
L28           11 S L7 NOT L27
                 SELECT RN L28 1-11

     FILE 'REGISTRY' ENTERED AT 09:44:59 ON 06 DEC 2000
L29           27 S E10-36

     FILE 'HCAPLUS' ENTERED AT 09:45:08 ON 06 DEC 2000
L30           10 S L28 AND L29
L31            1 S L28 NOT L30

     FILE 'REGISTRY' ENTERED AT 09:54:59 ON 06 DEC 2000
L32            0 S ALLOPREGNALONE/CN
                 E ALLOPREGNALONE/CN
                 E ALLOPREGNANOLONE/CN
L33            1 S E3
L34            1 S ALPHAXALONE/CN
L35            0 S ALPROZOLAM/CN
                 E ALPROZOLAM/CN
L36            1 S AMOBARBITAL/CN
L37            1 S APROBARBITAL/CN
L38            1 S AVERMECTIN B/CN
                 E BALOFEN/CN
                 E BACLOFEN/CN
L39            2 S E3-4
L40            1 S BICUCULLINE/CN
L41            1 S BUTALBITAL/CN
L42            1 S CAMAZEPAM/CN
L43            1 S CLOFLUBICYNE/CN
L44            0 S CHLORDIAZPOXIDE/CN
L45            1 S CHLORDIAZEPOXIDE/CN
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inventor search

L32 – L107 is the Registry search of the claimed cpds in Cl 2

L46	0	S	CLORAZEPAM/CN
		E	CLORAZEPAM/CN
		E	CLOROZEPAM/CN
		E	CLORAZ/CN
L47	3	S	E4-7
L48	1	S	BUTABARBITAL/CN
		E	DIAZEPAM/CN
L49	20	S	E13-20,E25-36
L50	0	S	DIHYFROEPIANDROSTERONE/CN
L51	0	S	DIHYDROEPIANDROSTERONE/CN
		E	DIHYDROEPIANDROSTERONE/CN
		E	DIHYDROANDROSTERONE/CN
		E	ANDROSTERONE/CN
L52	2	S	E57-58
L53	0	S	EPIALLOPREGNANOLONE/CN
		E	ALLOPREGNANOLONE/CN
L54	1	S	E3
		E	EPIPREGNANOLONE/CN
L55	1	S	E3
L56	1	S	ESTAZOLAM/CN
L57	0	S	ETBICUPHAT/CN
		E	ETBICUPHAT/CN
L58	1	S	E4
L59	0	S	ETOMIDTE/CN
L60	1	S	ETOMIDATE/CN
L61	1	S	LORAZEPAM/CN
L62	0	S	GLUNITRAZEPAM/CN
L63	1	S	FLUNITRAZEPAM/CN
L64	0	S	GLURAZEPAM/CN
L65	1	S	FLURAZEPAM/CN
L66	1	S	HALAZEPAM/CN
		E	HYDRASTINE/CN
L67	8	S	E3-12
L68	0	S	ISOBICPHAT/CN
		E	ISOBIC/CN
		E	BICPHAT/CN
		E	MEBICPHAT/CN
		E	MEBICYPHAT/CN
		E	BICYPHAT/CN
		E	ISOBICYPHAT/CN
L69	1	S	MEPHOBARBITAL/CN
L70	1	S	MIDAZOLAM/CN
L71	1	S	OXAZEPAM/CN
L72	1	S	PAGOCLONE/CN
L73	1	S	PENTOBARBITONE/CN
L74	1	S	PENTOBARBITAL/CN
L75	1	S	PHENOBARBITAL/CN
L76	1	S	PICROTOXININ/CN
L77	1	S	PICROTIN/CN
L78	1	S	PINAZEPAM/CN
L79	1	S	PRAZEPAM/CN
L80	2	S	PREGNANOLONE/CN
L81	1	S	PREGNENOLONE/CN
L82	1	S	PROGESTERONE/CN
L83	1	S	PROPOFOL/CN
		E	PROPYLB/CN
		E	PROPYLBIC/CN
L84	1	S	QUAZEPAM/CN
L85	1	S	SECOBARBITAL/CN
L86	1	S	SURICLONE/CN
L87	0	S	TENAZEPAM/CN
		E	TENAZEPAM/CN
		E	TENEZEPAM/CN
L88	0	S	TETRAHYDROOXYCORTICOSTERONE/CN
L89	0	S	TETRAHYDROXYCORTICOSTERONE/CN
		E	TETRAHYDROXYCORTICOSTERONE/CN
		E	CORTICOSTERONE/CN
		E	CORTICOSTERONE, TETRA/CN
L90	1	S	E4
		E	CORTICOSTERONE, OXY/CN

TEXT

=> d bib abs hitstr l31

L31 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2000 ACS
AN 1997:560510 HCAPLUS
DN 127:200446
TI Self-infusion of GABAA antagonists directly into the ventral tegmental area and adjacent regions
AU Ikemoto, Satoshi; **Murphy**, **James M.**; Mcbride, William J.
CS Department of Psychiatry, Indiana University School of Medicine, Indianapolis, IN, 46202-4887, USA
SO Behav. Neurosci. (1997), 111(2), 369-380
CODEN: BENEDJ; ISSN: 0735-7044
PB American Psychological Association
DT Journal
LA English
AB This study used an intracerebral self-administration paradigm in rats to det. if blockade of GABAA receptors in the ventral tegmental area (VTA) has a reinforcing effect. Rats quickly learned to self-infuse a picrotoxin soln. into the anterior VTA; rats discriminated the lever that produced picrotoxin infusions from the lever without consequences; and when the response requirement was increased, rats increased response levels for picrotoxin infusion. The reinforcing effect of picrotoxin was site-specific: Anterior VTA regions supported vigorous self-infusions, but not the posterior VTA, substantia nigra, or lateral hypothalamus. Muscimol, a GABAA agonist, disrupted picrotoxin self-infusion, but bicuculline, a GABAA antagonist, was self-infused into the VTA. The results suggest that blockade of GABAA receptors in the anterior VTA is reinforcing and that functional organization of the **GABA** systems within the VTA is heterogeneous.

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L91           0 S TETRAMETHYLENE SULFOTETRAMIDE/CN
L92           0 S SULFOTETRAMIDE/CN
                E SULFOTETRAMIDE/CN
                E SULFATETRAMIDE/CN
                E TETRAMIDE/CN
L93           1 S THIOPENTAL/CN
L94           1 S TRIAZOLAM/CN
L95           1 S ZOPICLONE/CN
                E SULFOTET/CN
                E GABA/CN
L96          21 S E17-41
                E .GAMMA.AMINOBUTYRIC ACID/CN

     FILE 'HCAPLUS' ENTERED AT 10:30:41 ON 06 DEC 2000
L97           4 S ALPROZOLAM
L98           4 S CLORAZEPAM
L99           7 S EPIALLOPREGNANOLONE
L100          0 S ETBICUPHAT
L101          0 S ETBICYPHAT
L102          0 S ISOBICYPHAT
L103          0 S MEBICYPHAT
L104          0 S PROPYLIBICPHAT
L105          0 S ?BICPHAT?
L106          1 S TENAZEPAM
                S TETRAHYDROEOXYCORTICOSTERONE/CN

     FILE 'REGISTRY' ENTERED AT 10:34:07 ON 06 DEC 2000
L107          0 S TETRAHYDROEOXYCORTICOSTERONE/CN

     FILE 'HCAPLUS' ENTERED AT 10:34:08 ON 06 DEC 2000
L108          0 S L107
L109          0 S TETRAHYDROEOXYCORTICOSTERONE
L110          1 S TETRAHYDROXYCORTICOSTERONE
L111          0 S SULFOTETRAMIDE
L112      10742 S .GAMMA.AMINOBUTYRIC ACID
L113      28058 S GABA
L114       9351 S (L112 OR L113)(3A)RECEPTOR
L115         27 S L96
L116       9352 S L114 OR L115
L117       8214 S L33-50
L118       5668 S L51-65
L119      57746 S L66-85
L120       2665 S L86-95
L121       3385 S STUTTER? OR SPEAK? OR ?SPEECH?
L122      33461 S GABA?
L123      13793 S L122(5A)?RECEPTOR?
L124      13942 S L116 OR L123
L125         38 S L124 AND (L121 OR VOCAL?)
L126       3002 S STAMMER? OR ?SPEAK?
L127        176 S L117-120 AND (L121 OR L126 OR ?VOCAL?)
L128         53 S L117-120 (L) (L121 OR L126 OR ?VOCAL?)
L129          2 S L128 AND PY>1999
L130         51 S L128 NOT L129
L131          6 S L130 AND L124
L132         45 S L130 NOT L131
L133          0 S (L86 OR L72) AND L130
L134          9 S L72
L135         65 S L86
L136         15 S L124 AND L134-135
L137          0 S L134-135 AND (L121 OR L126 OR ?VOCAL?)

     FILE 'REGISTRY' ENTERED AT 11:23:06 ON 06 DEC 2000
                SAVE L33-L95 HUI803C/L

     FILE 'USPATFULL' ENTERED AT 11:24:14 ON 06 DEC 2000
L138          2 S L72
L139          3 S L86
L140          5 S L138-139
L141     140405 S L121 OR L126 OR  ?VOCAL?
L142          0 S L140 AND L141
```

cites for claimed cpds in claim 2

6 cites for vocaliz?, ETC & GABA receptor

45 cites for speech ETC & named cpds

pagoclone cites

Suriclone cites

neither L134-135 cites are related to Speeeech ETC.

pagoclone patents

suriclone patent

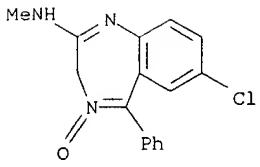
nothing related to speech ETC.

L143 611 S L124
L144 0 S L140 AND L143

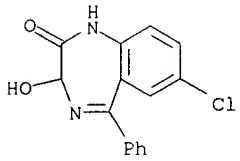
TEXT

=> d bib abs hitstr l131 1

L131 ANSWER 1 OF 6 HCAPLUS COPYRIGHT 2000 ACS
AN 1998:623543 HCAPLUS
DN 130:32904
TI Rat pup ultrasonic vocalization: effects of benzodiazepine receptor ligands
AU Olivier, Berend; Molewijk, Ellen; van Oorschot, Ruud; van der Heyden, Jan; Ronken, Eric; Mos, Jan
CS CNS Research, Solvay Pharmaceuticals, Weesp, 1380 DA, Neth.
SO Eur. J. Pharmacol. (1998), 358(2), 117-128
CODEN: EJPHAZ; ISSN: 0014-2999
PB Elsevier Science B.V.
DT Journal
LA English
AB The involvement of the **GABAA**-benzodiazepine **receptor** complex in rat pup ultrasonic vocalizations was studied by testing benzodiazepine receptor ligands with varying intrinsic activity and selectivity for benzodiazepine subtype receptors. Ultrasonic vocalizations were recorded under two temp. conditions (37.degree. and 18.degree.), presumably reflecting a low and high stress state. The latency to the neg. geotaxis response, a measure of motor coordination and the rectal temp. were detd. to assess putative side effects of drugs. The full, non-selective benzodiazepine receptor agonists diazepam, chlordiazepoxide, alprazolam and oxazepam suppressed ultrasonic vocalizations both at 37.degree. and 18.degree. conditions, although more efficaciously at 37.degree.. The partial, non-selective benzodiazepine receptor agonist bretazenil and the partial benzodiazepinel selective receptor agonist alpidem significantly reduced ultrasonic vocalizations at 37.degree., but not at 18.degree.. The full benzodiazepinel selective receptor agonist zolpidem behaved like other full, non-selective benzodiazepine receptor agonists by reducing ultrasonic vocalizations under both high and low temp. The effects of zolpidem indicate that activation of benzodiazepinel receptors alone already suffices to suppress ultrasonic vocalizations. The non-selective, benzodiazepine receptor antagonist flumazenil and the partial, non-selective benzodiazepine receptor inverse agonist FG 7142 and the full, non-selective benzodiazepine receptor inverse agonist DMCM (6,7-dimethoxy-4-ethyl-.beta.-carboline-3-carboxylate) had no significant effect on ultrasonic vocalizations under both temp. conditions. The involvement of benzodiazepine receptors in rat pup ultrasonic vocalizations (37.degree.-condition) was confirmed by antagonism of the ultrasonic vocalizations reducing effects of chlordiazepoxide by flumazenil (1 or 3 mg/kg). Using the rat pup ultrasonic vocalizations paradigm under 18.degree. and 37.degree. conditions combined with measurements of neg. geotaxis-latencies and rectal temps. it is possible to (1) distinguish benzodiazepine receptor agonists from other anxiolytics because of dissimilar dose response curves at 37.degree. and 18.degree., (2) differentiate partial from full receptor agonists by absence of effects at the 18.degree. condition, (3) suggest a key role for benzodiazepinel receptors in the modulation of ultrasonic vocalizations. These data contribute to the predictive validity of pup vocalizations as an animal model of anxiety.
IT **58-25-3**, Chlordiazepoxide **604-75-1**, Oxazepam
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(benzodiazepine receptor ligands effect on rat pup ultrasonic **vocalization** at room and cold temp.)
RN 58-25-3 HCAPLUS
CN 3H-1,4-Benzodiazepin-2-amine, 7-chloro-N-methyl-5-phenyl-, 4-oxide (9CI) (CA INDEX NAME)



RN 604-75-1 HCAPLUS
CN 2H-1,4-Benzodiazepin-2-one, 7-chloro-1,3-dihydro-3-hydroxy-5-phenyl- (7CI, 8CI, 9CI) (CA INDEX NAME)

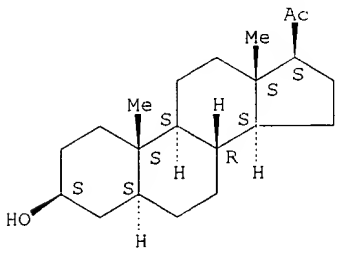


RE.CNT 68
RE
(4) Benton, D; Psychopharmacology 1988, V95, P99 HCAPLUS
(6) Brogden, R; Drugs 1991, V42, P1061 HCAPLUS
(8) Cagiano, R; Biol Psychiatry 1993, V17, P151 HCAPLUS
(10) Darragh, A; Psychopharmacology 1983, V80, P192 HCAPLUS
(13) File, S; Arch Int Pharmacodyn Ther 1984, V271, P198 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d bib abs hitstr l131 2

L131 ANSWER 2 OF 6 HCAPLUS COPYRIGHT 2000 ACS
AN 1997:458253 HCAPLUS
DN 127:145327
TI Ultrasonic vocalizations in rat pups: modulation at the .gamma.-aminobutyric acidA receptor complex and the neurosteroid recognition site
AU Vivian, Jeffrey A.; Barros, Helena M. T.; Manitiu, Andre; Miczek, Klaus A.
CS Dep. of Psychology, Tufts University, Medford, MA, 02155, USA
SO J. Pharmacol. Exp. Ther. (1997), 282(1), 318-325
CODEN: JPETAB; ISSN: 0022-3565
PB Williams & Wilkins
DT Journal
LA English
AB Agonists acting at benzodiazepine, .gamma.-aminobutyric acidA, barbiturate and neurosteroid recognition sites were studied for their attenuation of sepn.-induced ultrasonic vocalizations (USV) in rat pups. The behavioral effects of the neuroactive steroid 3.alpha.-hydroxy-5.alpha.-pregnan-20-one (allopregnanolone) were assessed when the drug was administered alone and in combination with agonists and antagonists acting at the .gamma.-aminobutyric acidA receptor complex. At 7 days postpartum, male and female Long-Evans rat pups were sepd. from the dam and littermates, and placed on a 20.degree. surface for 2 min. Allopregnanolone (1-30 mg/kg, s.c.), alprazolam (0.03-1 mg/kg, s.c.), diazepam (0.1-3 mg/kg, s.c.), muscimol (0.03-0.3 mg/kg, s.c.) and pentobarbital (1-30 mg/kg, s.c.) dose-dependently decreased USV. Pretreatment with flumazenil (0.1 mg/kg, s.c.) antagonized alprazolam's and diazepam's USV-suppressive effects; bicuculline (2 mg/kg, s.c.) reversed muscimol's USV-suppressive effects. Allopregnanolone (3 mg/kg, s.c.) produced a 4- to 7-fold leftward shift in alprazolam's and diazepam's USV-suppressive effects, and also produced a modest leftward shift in pentobarbital's USV dose-effect function. Nether flumazenil, bicuculline, nor picrotoxin (1 mg/kg, s.c.) altered allopregnanolone's USV-suppressive effects. These results suggest that the USV-suppressive effects of the neurosteroid allopregnanolone are mediated at the .gamma.-aminobutyric acidA receptor complex, and are independent from a direct action on the benzodiazepine or .gamma.-aminobutyric acidA recognition sites on this complex.
IT **516-55-2**, Allopregnanolone
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(ultrasonic **vocalization** modulation in rat pups at **GABAA receptor** and neurosteroid recognition site)
RN 516-55-2 HCAPLUS
CN Pregnan-20-one, 3-hydroxy-, (3.beta.,5.alpha.)- (9CI) (CA INDEX NAME)

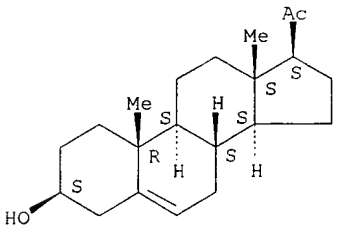
Absolute stereochemistry.



=> d bib abs hitstr l131 3

L131 ANSWER 3 OF 6 HCAPLUS COPYRIGHT 2000 ACS
AN 1997:9696 HCAPLUS
DN 126:100531
TI Prenatal alcohol exposure influences the effects of neuroactive steroids on separation-induced ultrasonic vocalizations in rat pups
AU Zimmerberg, Betty; McDonald, Brenna C.
CS Department Psychology, Williams College, Williamstown, MA, 01267, USA
SO Pharmacol., Biochem. Behav. (1996), 55(4), 541-547
CODEN: PBBHAU; ISSN: 0091-3057
PB Elsevier
DT Journal
LA English
AB Fetal alc. exposure has been reported to be assocd. with hyper-responsiveness to stress. Using a maternal sepn. paradigm, this study examd. whether prenatal alc. exposure affected sensitivity to neurosteroid modulation of stress. The authors have shown that the neuroactive steroid allopregnanolone reduces ultrasonic vocalizations (USVs) after brief maternal sepn. in week-old rat pups. Prenatal alc. exposure, however, resulted in reduced sensitivity to this neurosteroid. In this study's first expt., the behavioral effects of pregnenolone sulfate, a neurosteroid with reportedly opposite modulatory effects on the **GABAA receptor**, were characterized. Pregnenolone sulfate had a triphasic effect on the prodn. of ultrasonic vocalizations and on open field activity. Blockade of conversion of pregnenolone sulfate to allopregnanolone via the 5.alpha.-reductase inhibitor 4-MA also blocked the drug-related redn. in USVs, but not the higher-dose augmentation. The enzyme inhibitor alone had no significant effects on USV prodn., nor did progesterone. These results suggest that the neuroactive steroid pregnenolone sulfate may play an independent role in the stress response after maternal sepn. as well as being a precursor for the anxiolytic neurosteroid allopregnanolone. In the second expt., prenatal alc. exposure was found to eliminate both the low dose USV-reducing effect and the higher dose USV-increasing effect. These results support previous results demonstrating that prenatal alc. exposure may cause an altered sensitivity to the neuromodulatory effects of neurosteroids.
IT **145-13-1**, Pregnenolone
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(prenatal alc. exposure influences the effects of neuroactive steroids on sepn.-induced ultrasonic **vocalizations** in rat pups)
RN 145-13-1 HCAPLUS
CN Pregn-5-en-20-one, 3-hydroxy-, (3.beta.)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



=> d bib abs hitstr l131 4

L131 ANSWER 4 OF 6 HCAPLUS COPYRIGHT 2000 ACS
AN 1987:962 HCAPLUS
DN 106:962
TI Influence of adrenoblockers on antinociceptive effect of GABA-positive drugs
AU Andreev, B. V.; Ignatov, Yu. D.
CS I. P. Pavlov 1st Med. Inst., Leningrad, USSR
SO Byull. Eksp. Biol. Med. (1986), 102(10), 438-40
CODEN: BEBMAE; ISSN: 0365-9615
DT Journal
LA Russian
AB Expts. in rats indicated that selective .alpha.1- and .alpha.2-adrenergic blockers (prazosin and yohimbine, resp.) and the dopamine hydroxylase inhibitor FD-008 did not alter the antinociceptive action of baclofen [**1134-47-0**] (a **GABAergicB receptor** agonist). All 3 blockers reduced the antinociceptive action of THIP [64603-91-4] and depakine [99-66-1] (**GABAergicA receptor** agonists) in a **vocalization** test. However, in the tail-flick test the analgesic effects of THIP and depakine were not affected by prazosin or FD-008 but were increased by yohimbine. The role of adrenergic mechanisms in **GABAergicA** and **GABAergicB receptor** -mediated analgesia is discussed.

=> d bib abs hitstr l131 5

L131 ANSWER 5 OF 6 HCAPLUS COPYRIGHT 2000 ACS
AN 1986:564846 HCAPLUS
DN 105:164846
TI Sedative-hypnotic anomalies related to dose of pentobarbital in long-sleep and short-sleep selectively-bred mice
AU Alpern, Herbert P.; McIntyre, Todd D.
CS Dep. Psychol., Univ. Colorado, Boulder, CO, 80309, USA
SO Pharmacol., Biochem. Behav. (1986), 25(2), 333-6
CODEN: PBBHAU; ISSN: 0091-3057
DT Journal
LA English
AB Hypnotic effects following administration of 3 doses of pentobarbital [**76-74-4**] were evaluated in mice selectively-bred for differential hypnotic sensitivity to EtOH [64-17-5]. Although the EtOH sensitive Long-Sleep (LS) line displays greater sedation to a wide variety of central nervous system depressant when compared to the EtOH-insensitive Short-Sleep (SS) line, the response pattern to pentobarbital remains **equivocal**. Thus, to clarify the effect of pentobarbital, certain variables (dose, sex, circadian rhythmicity) believed to be important in the expression of sleep time were evaluated. For all doses examd. "sex" and "time of day tested" impacted on sleep time. With these provisos, 40 mg/kg consistently induced shorter sleep time in SS mice. The 60 mg/kg dose either failed to distinguish these 2 lines, or induced greater sleep times in the SS mice. The 80 mg/kg dose tended to have the same effect as the 60 mg/kg dose, but to a greater degree. Overall, it appears that for each line the dose response curve for pentobarbital is sigmoidal, but that the slope of the curve for the middle range of doses is greater for the SS line. Since pentobarbital has a unique effect on these lines of mice that is dissimilar to those reported for other barbiturates, the implication is that an addnl. factor, that is unimportant for other barbiturates, is essential for pentobarbital-induced hypnosis. Factors that could be responsible for this effect include differential metab. or **GABAergic receptor** dynamics.

=> d bib abs hitstr l131 6

L131 ANSWER 6 OF 6 HCAPLUS COPYRIGHT 2000 ACS
AN 1982:575784 HCAPLUS
DN 97:175784
TI Enhancing GABAergic transmission reverses the aversive state in rats induced by electrical stimulation of the periaqueductal grey region
AU Bovier, Phillipe; Broekkamp, Chris L. E.; Lloyd, Kenneth G.
CS LERS-Synthelabo, Bagneux, 92 220, Fr.
SO Brain Res. (1982), 248(2), 313-20
CODEN: BRREAP; ISSN: 0006-8993
DT Journal
LA English
AB In a proposed rat model for anxiety (elec. stimulation of the periaqueductal grey region), progabide [62666-20-0] (a GABA agonist) and diazepam [439-14-5] both increased the latency to escape to a safe compartment and also the current needed to induce the escape response (escape threshold). Furthermore, the effects of progabide and diazepam were greater than additive in their actions on the escape response; when given together in normally subliminal doses, the combination exerted a marked anti-aversive effect. These actions of the drugs alone or in combination could not be explained by non-specific motor effects. Blockade of **GABA receptors** by bicuculline [**485-49-4**] greatly reduced or abolished the action of progabide and diazepam (single administration). sodium valproate [1069-66-5], Which indirectly augments GABAergic transmission, also increased the escape latency and escape threshold; in contrast, diphenylhydantoin [57-41-0] accentuated the aversive effects of stimulation of the periaqueductal grey. haloperidol [52-86-8] Increased the escape latency and threshold but not other signs of distress following central stimulation (**vocalization**, jumping) which were effectively blocked by progabide and diazepam. The action of haloperidol was completely explicable by an interference with motor mechanisms. These results are interpreted as an indication that GABA agonists have an anti-aversive action in this proposed rat model for anxiety and, further-more, that **GABA receptors** at least partially mediate the actions of benzodiazepines in this model.

TEXT

=> d bib abs hitstr l27

L27 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2000 ACS
AN 1985:215899 HCAPLUS
DN 102:215899
TI Release of endogenous dopamine, 3,4-dihydroxyphenylacetic acid, and amino acid transmitters from rat striatal slices
AU Flint, R. S.; **Murphy, J. M.**; McBride, W. J.
CS Sch. Med., Indiana Univ., Indianapolis, IN, 46223, USA
SO Neurochem. Res. (1985), 10(4), 515-27
CODEN: NEREDZ; ISSN: 0364-3190
DT Journal
LA English
AB The release of endogenous dopamine (DA) [**51-61-6**] and 3,4-dihydroxyphenylacetic acid (DOPAC) [**102-32-9**] was measured in superfused striatal slices of the rat, and the results were compared with data obtained for the release of endogenous (a) DA and DOPAC in the cerebral cortex, nucleus accumbens and thalamus; (b) 5-hydroxytryptamine (5-HT) [**50-67-9**], 5-**hydroxyindoleacetic** acid (5-HIAA) [**54-16-0**], **GABA** [**56-12-2**], and glutamate [**56-86-0**] in the striatum; and (c) **GABA**, glutamate, and 5-HT in the cerebral cortex. In superfused slices of all 4 central nervous system regions, there was a Ca2+-dependent, K+-stimulated release of endogenous DA. In addn., in slices of the striatum and nucleus accumbens there was a Ca2+-dependent, K+-stimulated release of endogenous DOPAC. In the striatum, Mg2+ was as effective as Ca2+ in promoting the K+-stimulated release of DOPAC. In addn., Mg2+ appeared to function as a weak Ca2+ agonist since it also promoted the release of DA to approx. 40% of the level attained with Ca2+ in the presence of K+. However, in the striatum, Mg2+ inhibited the Ca2+-dependent, K+-stimulated release of **GABA** and glutamate. Similar Mg2+-inhibition was obsd. in the cerebral cortex not only for **GABA** and glutamate but also for DA and 5-HT. The use of .alpha.-Me p-tyrosine (tyrosine hydroxylase inhibitor), cocaine (uptake inhibitor), and pargyline (monoamine oxidase inhibitor) indicated that most of the released DA and DOPAC was synthesized in the slices during the superfusion, that DOPAC was not formed from DA which had been released and taken up, and that DA and DOPAC were released from DA nerve terminals. In addn., there was a difference in the release process between the amino acids and the monoamines from striatal slices since Mg2+ inhibited the Ca2+-dependent, K+-stimulated release of **GABA** and glutamate and appeared to promote the release of DA and 5-HT.
IT **7439-95-4**, biological studies **7440-09-7**, biological studies **7440-70-2**, biological studies
RL: BIOL (Biological study)
(neurotransmitter release by brain regions response to)
RN 7439-95-4 HCAPLUS
CN Magnesium (8CI, 9CI) (CA INDEX NAME)

Mg

RN 7440-09-7 HCAPLUS
CN Potassium (8CI, 9CI) (CA INDEX NAME)

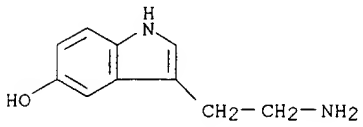
K

RN 7440-70-2 HCAPLUS
CN Calcium (8CI, 9CI) (CA INDEX NAME)

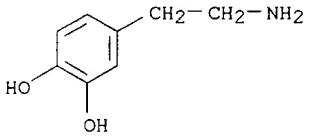
Ca

IT **50-67-9**, biological studies **51-61-6**, biological studies **54-16-0**, biological studies **56-12-2**, biological studies

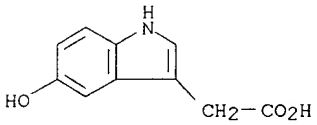
56-86-0, biological studies **102-32-9**
RL: BIOL (Biological study)
(release of, by brain regions, cations effect on)
RN 50-67-9 HCAPLUS
CN 1H-Indol-5-ol, 3-(2-aminoethyl)- (9CI) (CA INDEX NAME)



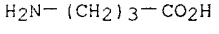
RN 51-61-6 HCAPLUS
CN 1,2-Benzenediol, 4-(2-aminoethyl)- (9CI) (CA INDEX NAME)



RN 54-16-0 HCAPLUS
CN 1H-Indole-3-acetic acid, 5-hydroxy- (9CI) (CA INDEX NAME)

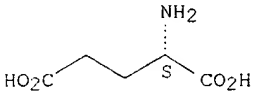


RN 56-12-2 HCAPLUS
CN Butanoic acid, 4-amino- (9CI) (CA INDEX NAME)

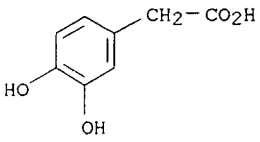


RN 56-86-0 HCAPLUS
CN L-Glutamic acid (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 102-32-9 HCAPLUS
CN Benzeneacetic acid, 3,4-dihydroxy- (9CI) (CA INDEX NAME)

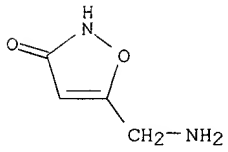


=> d bib abs hitstr l30 1

L30 ANSWER 1 OF 10 HCAPLUS COPYRIGHT 2000 ACS
AN 1998:638342 HCAPLUS
DN 129:340756
TI Blocking GABAA receptors in the anterior ventral tegmental area attenuates ethanol intake of the alcohol-preferring P rat
AU Nowak, K. L.; McBride, W. J.; Lumeng, L.; Li, T.-K.; **Murphy, J. M.**
CS Department of Psychiatry, Institute of Psychiatric Research, Indiana University School of Medicine, Indianapolis, IN, 46202-4887, USA
SO Psychopharmacology (Berlin) (1998), 139(1/2), 108-116
CODEN: PSCHDL; ISSN: 0033-3158
PB Springer-Verlag
DT Journal
LA English
AB The effect of blocking the A subtype of .gamma.-aminobutyric acid (GABAA) receptors in the anterior ventral tegmental area (VTA) on ethanol (EtOH; 10% vol./vol.) and saccharin (SACC; 0.0125%) consumption was investigated in alc.-preferring P rats. Picrotoxin (0.005, 0.01, 0.05 and 0.10 .mu.g/0.5 .mu.l) was injected into the VTA, and consumption of EtOH and SACC was assessed in two 2-h limited-access drinking paradigms (concurrent EtOH/SACC access, and alternate-day-access to EtOH and SACC). Under concurrent-access conditions, the picrotoxin microinjections resulted in a 55 and 84% decrease in EtOH consumption at the 0.05 and 0.10 .mu.g doses, resp., compared with consumption following microinjections of vehicle soln. Saccharin intake was not significantly altered by picrotoxin. Under alternate-day-access drinking conditions, the picrotoxin microinjections resulted in dose-dependent decreases in EtOH consumption of 37-68%, with significant decreases following the 0.005, 0.05 and 0.10 .mu.g doses. Saccharin intake was significantly reduced only at the 0.05 .mu.g dose. The decrease in EtOH consumption after 0.10 .mu.g picrotoxin was attenuated by co-administration of 0.01 .mu.g muscimol. This dose of muscimol had no effect on EtOH consumption when injected alone. Intra-VTA injections of bicuculline (0.04 .mu.g), another GABAA antagonist, reduced EtOH intake, comparable to the redn. following 0.10 .mu.g picrotoxin. Microinjections of 0.10 .mu.g picrotoxin in regions outside the VTA failed to decrease EtOH intake. These results suggest that anterior VTA mechanisms regulating alc. drinking behavior are under tonic **GABA** inhibition, mediated by GABAA receptors. The results also suggest that different neural mechanisms are regulating voluntary EtOH and SACC drinking behaviors.
IT **64-17-5**, Ethanol, biological studies
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(GABAA receptors blockade in anterior ventral tegmental area attenuates ethanol intake of alc.-preferring P rat)
RN 64-17-5 HCAPLUS
CN Ethanol (9CI) (CA INDEX NAME)

=> d bib abs hitstr l30 2

L30 ANSWER 2 OF 10 HCAPLUS COPYRIGHT 2000 ACS
AN 1998:542248 HCAPLUS
DN 129:239819
TI Regional differences within the rat ventral tegmental area for muscimol self-infusions
AU Ikemoto, Satoshi; **Murphy**, **James M.**; McBride, William J.
CS Institute of Psychiatric Research, Department of Psychiatry, Indiana University School of Medicine, Indianapolis, IN, 46202-4887, USA
SO Pharmacol., Biochem. Behav. (1998), 61(1), 87-92
CODEN: PBBHAU; ISSN: 0091-3057
PB Elsevier Science Inc.
DT Journal
LA English
AB The present study examd. the effects of activating GABAA receptors in the anterior and posterior regions of the ventral tegmental area (VTA) on operant reinforcement behavior, using the technique of intracranial self-administration. Rats were given the opportunity to self-administer vehicle alone (artificial CSF) and vehicle contg. 25.50, and 100 .mu.M muscimol, a GABAA agonist, into the anterior or posterior VTA during four sessions (3 h/session) in std. two-lever operant chambers. Rats received five times greater infusions of 50 and 100 .mu.M muscimol than vehicle into the posterior VTA: both doses significantly increased responding above vehicle levels on the active and inactive (control) levers equally. When the response requirement for muscimol infusions was increased from a fixed-ratio 1 (FR1) to FR3 in a single-lever chamber, the total session responses increased approx. twofold. Muscimol was not self-infused when cannula placements were in the anterior VTA. The self-infusion of muscimol into the posterior VTA was attenuated by coadministration of picrotoxin. Overall, the results suggest that the activation of GABAA receptors in the posterior VTA produces goal-directed behavior.
IT **2763-96-4**, Muscimol
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(muscimol self-infusion by rats into anterior vs. posterior ventral tegmental)
RN 2763-96-4 HCAPLUS
CN 3(2H)-Isoxazolone, 5-(aminomethyl)- (9CI) (CA INDEX NAME)



=> d bib abs hitstr l30 3

L30 ANSWER 3 OF 10 HCAPLUS COPYRIGHT 2000 ACS
AN 1995:782709 HCAPLUS
DN 123:246564
TI Effects of negative modulators of GABAergic efficacy on ethanol intake: correlation of biochemical changes with pharmacological effect using a behavioral paradigm
AU June, Harry L.; Lin, Margaret; Greene, Terri L.; Lewis, Michael J.; **Murphy, James M.**
CS Department of Psychology, Indiana University-Purdue University, Indianapolis, IN, 46202-3275, USA
SO Exp. Clin. Psychopharmacol. (1995), Volume Date 1995, 3(3), 252-60
CODEN: ECLPES
DT Journal
LA English
AB Neg. allosteric modulators of varying intrinsic efficacies that reduce GABAergic function were evaluated for the ability to decrease the reinforcing properties of ethanol (EtOH) in the selectively bred alc.-preferring (P) rats. Pretreatment with neg. modulators maximally reduced EtOH intake during the initial 15-min interval to 9-49% of control levels; however, rank-order potencies of neg. modulators to attenuate EtOH intake were not correlated with rank-order potencies of neg. modulators to inhibit .gamma.-amino-butyric acid (**GABA**) 36Cl- conductance and enhance 35S-t-butylbicyclophosphorothionate (TBPS) binding. Thus, the underlying mechanism mediating inhibition of EtOH intake and inhibition of 36Cl- conductance or enhanced TBPS ratios may not be identical. The ability of inverse agonists to modify the reinforcing actions of EtOH may be related to their affinity at different GABAA-benzodiazepine receptor subtypes.
IT **64-17-5**, Ethanol, biological studies
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(GABAA-benzodiazepine receptors in modulation of reinforcing actions of EtOH)
RN 64-17-5 HCAPLUS
CN Ethanol (9CI) (CA INDEX NAME)

H_3C-CH_2-OH

IT **56-12-2**, .gamma.-Amino-butyric acid, biological studies
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BIOL (Biological study); PROC (Process)
(GABAA-benzodiazepine receptors in modulation of reinforcing actions of EtOH)
RN 56-12-2 HCAPLUS
CN Butanoic acid, 4-amino- (9CI) (CA INDEX NAME)

$H_2N-(CH_2)_3-CO_2H$

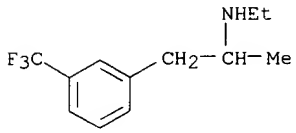
=> d bib abs hitstr l30 4

L30 ANSWER 4 OF 10 HCAPLUS COPYRIGHT 2000 ACS
AN 1992:145966 HCAPLUS
DN 116:145966
TI Serotonin, dopamine and **GABA** involvement in alcohol drinking of selectively bred rats
AU McBride, W. J.; **Murphy**, J. M.; Lumeng, L.; Li, T. K.
CS Sch. Med., Indiana Univ., Indianapolis, IN, 46202-4887, USA
SO Alcohol (N. Y.) (1990), 7(3), 199-205
CODEN: ALCOEX; ISSN: 0741-8329
DT Journal
LA English
AB Neurochem. and neuropharmacol. studies were undertaken to assess the involvement of central nervous system (CNS) serotonin (5-HT), dopamine (DA), and **GABA** systems in regulating the alc.-drinking behavior of 2 lines of rats selectively bred for their high alc.-seeking behavior, namely the alc.-preferring P line and the high alc.-drinking HAD line of rats. Neurochem. data indicate that high alc.-seeking behavior (when compared with data from rats with low alc.-seeking characteristics) is assocd. with: (a) lower (10-20%) contents of 5-HT in certain limbic regions (e.g., nucleus accumbens, frontal cortex, hypothalamus, and hippocampus); (b) a lower (10-15%) content of DA in the nucleus accumbens; (c) higher (20-35%) densities of 5-HT1A binding sites in some limbic regions (e.g., medial nucleus accumbens, medial prefrontal cortex, and ventral hippocampus); and (d) a greater (20-50%) d. of **GABA** axon terminals in the nucleus accumbens. Furthermore, the acute administration of high doses of ethanol appears to increase the activity of the 5-HT and DA projections to the nucleus accumbens of the P line of rats (as indicated by the 20-30% elevated tissue levels of 5-HT and DA metabolites following i.p. ethanol administration); neuronal tolerance to alc. appears to develop in both these monoamine pathways, as suggested by an attenuated effect on metabolite levels by a challenge dose of ethanol given to P rats that had been chronically drinking alc. The i.p. administration of agents which can increase the physiol. active pool of 5-HT (e.g., fluoxetine, an uptake inhibitor; fenfluramine, a releaser; and D,L-5-hydroxytryptophan, an immediate precursor) or which can mimic 5-HT (e.g., 5-HT1 and 5-HT2 agonists) all significantly decreased the volitional alc. intake of the high alc.-seeking rats. Similarly, the i.p. administration of a DA uptake inhibitor, DA releaser, or D2 agonist also reduced the volitional oral intake of alc. by the P line of rats. In addn., the consumption of alc. by the P line of rats is reduced by i.p. administration of Ro 15-4513, an inverse agonist at the GABAA-benzodiazepine-Cl- receptor complex. Overall, the data suggest that abnormalities exist in certain 5-HT, DA, and **GABA** systems in the CNS of P and HAD rats and that these abnormal transmitter systems may be major underlying biol. factors contributing to their high alc.-seeking characteristics. A hypothesis is offered to explain the involvement of the 5-HT, DA, and **GABA** systems of the nucleus accumbens in regulating alc. drinking of the selectively bred P and HAD lines of rats.
IT **64-17-5**, Ethanol, biological studies
RL: BIOL (Biological study)
(consumption of, dopamine and **GABA** and serotonin involvement in, selective breeding in relation to)
RN 64-17-5 HCAPLUS
CN Ethanol (9CI) (CA INDEX NAME)

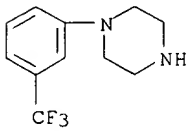
H_3C-CH_2-OH

IT **114-03-4** **458-24-2**, Fenfluramine **15532-75-9**, TFMPP **54910-89-3**, Fluoxetine **78950-78-4**, 8-OH DPAT **82830-53-3**, DOI
RL: BIOL (Biological study)
(ethanol consumption response to)
RN 114-03-4 HCAPLUS
RN 458-24-2 HCAPLUS

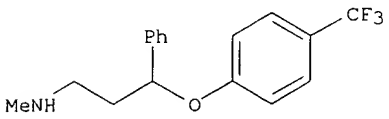
CN Benzeneethanamine, N-ethyl-.alpha.-methyl-3-(trifluoromethyl)- (9CI) (CA INDEX NAME)



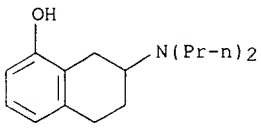
RN 15532-75-9 HCAPLUS
CN Piperazine, 1-[3-(trifluoromethyl)phenyl]- (9CI) (CA INDEX NAME)



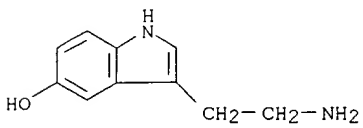
RN 54910-89-3 HCAPLUS
CN Benzenepropanamine, N-methyl-.gamma.-[4-(trifluoromethyl)phenoxy]- (9CI) (CA INDEX NAME)



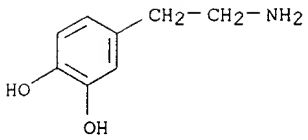
RN 78950-78-4 HCAPLUS
CN 1-Naphthalenol, 7-(dipropylamino)-5,6,7,8-tetrahydro- (9CI) (CA INDEX NAME)



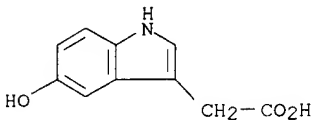
RN 82830-53-3 HCAPLUS
IT **50-67-9**, Serotonin, biological studies **51-61-6**, Dopamine, biological studies **54-16-0**, 5-HIAA, biological studies **56-12-2**, **GABA**, biological studies **102-32-9**, DOPAC **306-08-1**, Homovanillic acid
RL: BIOL (Biological study)
(of brain, ethanol effect on, after consumption, selective breeding in relation to)
RN 50-67-9 HCAPLUS
CN 1H-Indol-5-ol, 3-(2-aminoethyl)- (9CI) (CA INDEX NAME)



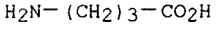
RN 51-61-6 HCAPLUS
CN 1,2-Benzenediol, 4-(2-aminoethyl)- (9CI) (CA INDEX NAME)



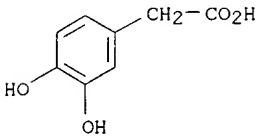
RN 54-16-0 HCAPLUS
CN 1H-Indole-3-acetic acid, 5-hydroxy- (9CI) (CA INDEX NAME)



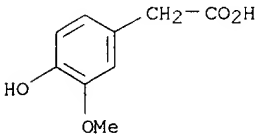
RN 56-12-2 HCAPLUS
CN Butanoic acid, 4-amino- (9CI) (CA INDEX NAME)



RN 102-32-9 HCAPLUS
CN Benzeneacetic acid, 3,4-dihydroxy- (9CI) (CA INDEX NAME)

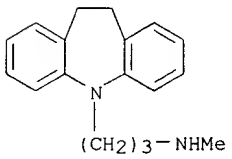


RN 306-08-1 HCAPLUS
CN Benzeneacetic acid, 4-hydroxy-3-methoxy- (9CI) (CA INDEX NAME)

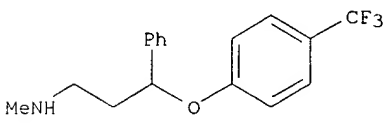


=> d bib abs hitstr l30 5

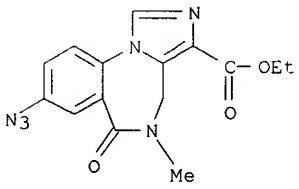
L30 ANSWER 5 OF 10 HCAPLUS COPYRIGHT 2000 ACS
AN 1988:604850 HCAPLUS
DN 109:204850
TI Effects of Ro 15-4513, fluoxetine and desipramine on the intake of ethanol, water and food by the alcohol-preferring (P) and -nonpreferring (NP) lines of rats
AU McBride, W. J.; **Murphy**, J. M.; Lumeng, L.; Li, T. K.
CS Sch. Med., Indiana Univ., Indianapolis, IN, 46233, USA
SO Pharmacol., Biochem. Behav. (1988), 30(4), 1045-50
CODEN: PBBHAU; ISSN: 0091-3057
DT Journal
LA English
AB The effects of i.p. administration of Ro 15-4513 (1, 2, and 4 mg/kg), fluoxetine (5 and 10 mg/kg), and despipramine (5 and 10 mg/kg) on the intake of 10% ethanol, H2O, and food were detd. in the selectively bred alc.-preferring (P) and -nonpreferring (NP) lines of rats with the daily access to fluids being limited to single 2-h sessions. The imidazobenzodiazepine Ro 15-4513 (a partial inverse benzodiazepine agonist) reduced the intake of 10% ethanol by P rats to 50-60% of control levels in the 1st 30 min without altering food or H2O intake. The attenuating actions of 2 mg/kg Ro 15-4513 on ethanol intake could be completely blocked by the benzodiazepine receptor antagonist Ro 15-1788 (10 mg/kg). Ro 15-1788, by itself, produced no effects on alc. and H2O consumption. The 5 mg/kg dose of fluoxetine reduced 10% ethanol intake by P rats to 20% of control values without altering either H2O or food consumption. The 10 mg/kg dose of fluoxetine further reduced ethanol intake by P rats, but this dose also reduced daily food intake to approx. 70% of normal. Desipramine at both doses reduced both ethanol and food uptake by P rats and had a tendency to reduce H2O consumption as well. In general, the 3 drugs had effects in the NP rats similar to those obsd. for the P group, although the effects on 10% ethanol intake were difficult to compare because of the low, variable intake of alc. by the NP group. The data are consistent with the involvement of serotonin and the **GABA** -benzodiazepine receptor complex in alc. drinking behavior.
IT **50-47-5**, Desipramine **54910-89-3 91917-65-6**
RL: BIOL (Biological study)
(ethanol and water and food intake response to)
RN 50-47-5 HCAPLUS
CN 5H-Dibenz[b,f]azepine-5-propanamine, 10,11-dihydro-N-methyl- (9CI) (CA INDEX NAME)



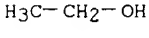
RN 54910-89-3 HCAPLUS
CN Benzenepropanamine, N-methyl-.gamma.-[4-(trifluoromethyl)phenoxy]- (9CI) (CA INDEX NAME)



RN 91917-65-6 HCAPLUS
CN 4H-Imidazo[1,5-a][1,4]benzodiazepine-3-carboxylic acid, 8-azido-5,6-dihydro-5-methyl-6-oxo-, ethyl ester (9CI) (CA INDEX NAME)



IT **64-17-5**, Ethanol, biological studies
RL: BIOL (Biological study)
(intake of, desipramine and fluoxetine and Ro 15-4513 effect on)
RN 64-17-5 HCAPLUS
CN Ethanol (9CI) (CA INDEX NAME)



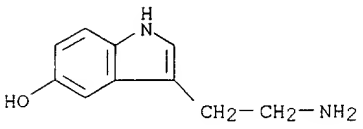
IT **7732-18-5**
RL: BIOL (Biological study)
(water drinking, desipramine and fluoxetine and Ro 15-4513 effect on)
RN 7732-18-5 HCAPLUS
CN Water (8CI, 9CI) (CA INDEX NAME)

=> d bib abs hitstr l30 6

L30 ANSWER 6 OF 10 HCAPLUS COPYRIGHT 2000 ACS
AN 1986:202126 HCAPLUS
DN 104:202126
TI Effects of ethanol on monoamine and amino acid release from cerebral cortical slices of the alcohol-preferring P line of rats
AU McBride, W. J.; **Murphy**, J. M.; Lumeng, L.; Li, T. K.
CS Sch. Med., Indiana Univ., Indianapolis, IN, 46223, USA
SO Alcohol.: Clin. Exp. Res. (1986), 10(2), 205-8
CODEN: ACRSDM; ISSN: 0145-6008
DT Journal
LA English
AB The effects of 250 mg/100 mL EtOH [**64-17-5**] on the efflux of DOPAC [**102-32-9**] and the 35 mM K+-stimulated, Ca2+-dependent release of norepinephrine (NE) [**51-41-2**], dopamine (DA) [**51-61-6**], 5-HT [**50-67-9**], **GABA** [**56-12-2**], glutamate [**56-86-0**], and aspartate [**56-84-8**] from cerebral cortical slices of the alc.-preferring P line of rats and stock rats were studied. The K+-stimulated, Ca2+-dependent release of **GABA** for the P rats was 35% lower, whereas the release of glutamate was almost twice that of the stock animals. The release of the other compds. was similar for the 2 groups. Addn. of 250 mg/100 mL EtOH to the superfusion media did not alter the release of NE, DA, and 5-HT nor the efflux of DOPAC from cortical slices of either group of rats. However, the K+-stimulated, Ca2+-dependent release of **GABA**, glutamate, and aspartate was significantly enhanced by EtOH for both the P and stock group of rats. These in vitro data do not support a direct action of EtOH on DA, NE, and 5-HT release or on DOPAC efflux, but suggest a direct action on te transmitter release process for **GABA**, glutamate, and aspartate in the cerebral cortex.
IT **64-17-5**, biological studies
RL: BIOL (Biological study)
(amino acids and monoamines release by cerebral cortex response to)
RN 64-17-5 HCAPLUS
CN Ethanol (9CI) (CA INDEX NAME)

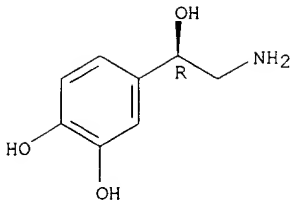
H_3C-CH_2-OH

IT **50-67-9**, biological studies **51-41-2** **51-61-6**, biological studies **56-12-2**, biological studies **56-84-8**, biological studies **56-86-0**, biological studies **102-32-9**
RL: BIOL (Biological study)
(of cerebral cortex, ethanol effect on release of, genetics in relation to)
RN 50-67-9 HCAPLUS
CN 1H-Indol-5-ol, 3-(2-aminoethyl)- (9CI) (CA INDEX NAME)

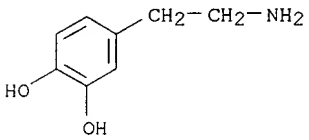


RN 51-41-2 HCAPLUS
CN 1,2-Benzenediol, 4-[(1R)-2-amino-1-hydroxyethyl]- (9CI) (CA INDEX NAME)

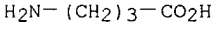
Absolute stereochemistry.



RN 51-61-6 HCAPLUS
CN 1,2-Benzenediol, 4-(2-aminoethyl)- (9CI) (CA INDEX NAME)

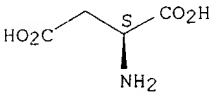


RN 56-12-2 HCAPLUS
CN Butanoic acid, 4-amino- (9CI) (CA INDEX NAME)



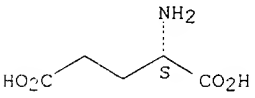
RN 56-84-8 HCAPLUS
CN L-Aspartic acid (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

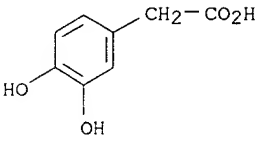


RN 56-86-0 HCAPLUS
CN L-Glutamic acid (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 102-32-9 HCAPLUS
CN Benzeneacetic acid, 3,4-dihydroxy- (9CI) (CA INDEX NAME)



=> d bib abs hitstr l30 7

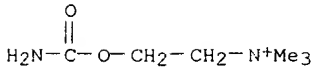
L30 ANSWER 7 OF 10 HCAPLUS COPYRIGHT 2000 ACS
AN 1985:535862 HCAPLUS
DN 103:135862
TI Monoamine, amino acid and cholinergic interactions in slices of rat cerebral cortex
AU Flint, R. S.; **Murphy**, J. M.; Calkins, P. M.; McBride, W. J.
CS Sch. Med., Indiana Univ., Indianapolis, IN, 46223, USA
SO Brain Res. Bull. (1985), 15(2), 197-202
CODEN: BRBUDU; ISSN: 0361-9230
DT Journal
LA English
AB Interactions of monoamine, amino acid, and cholinergic transmitter systems were studied in slices of rat cerebral cortex using a superfusion procedure and measuring release of endogenous dopamine (DA) [**51-61-6**], norepinephrine (NE) [**51-41-2**], serotonin (5-HT) [**50-67-9**], **GABA** [**56-12-2**], glutamate (GLU) [**56-86-0**], and aspartate (ASP) [**56-84-8**]. Depolarizing concns. of K+ were used to induce a Ca2+-dependent, Mg2+-inhibited release of the monoamines and amino acids. Submaximal release of the monoamines and amino acids was obsd. at 35 mM K+, which permitted studies of possible excitatory or inhibitory actions of the added agents. The 35 mM K+-stimulated, Ca2+-dependent release of **GABA** was inhibited 40, 30, and 25% by 100 .mu.M NE, DA, and 5-HT, resp. The release of GLU was potentiated by NE and reduced by DA. Both DA and 5-HT inhibited the release of ASP. The Ca2+-dependent, K+-stimulated release of endogenous NE, DA, and 5-HT was not altered by 100 .mu.M **GABA**, GLU, or ASP. However, 100 .mu.M GLU did enhance the stimulated release of **GABA**. The cholinergic agonist carbachol [**51-83-2**] enhanced the stimulated release of NE, 5-HT, and GLU 10, 60, and 40%, resp. On the other hand, carbachol attenuated the release of DA and **GABA** .apprx.20%. Apparently, the amino acid transmitter pathways in slices of the cerebral cortex of the rat can be controlled by monoaminergic and cholinergic systems, whereas the monoamine afferents appear to have a cholinergic regulation but not a major direct amino acid transmitter influence.
IT **7439-95-4**, biological studies **7440-70-2**, biological studies
RL: BIOL (Biological study)
(amino acids and monoamines release by brain cortex regulation by)
RN 7439-95-4 HCAPLUS
CN Magnesium (8CI, 9CI) (CA INDEX NAME)

Mg

RN 7440-70-2 HCAPLUS
CN Calcium (8CI, 9CI) (CA INDEX NAME)

Ca

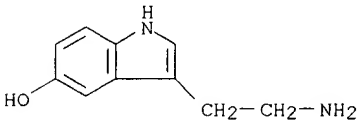
IT **51-83-2**
RL: BIOL (Biological study)
(amino acids and monoamines release by brain cortex response to)
RN 51-83-2 HCAPLUS
CN Ethanaminium, 2-[(aminocarbonyl)oxy]-N,N,N-trimethyl-, chloride (9CI) (CA INDEX NAME)



IT **7440-09-7**, biological studies
RL: BIOL (Biological study)
(amino acids and monoamines release by brain cortex stimulation by, regulation of)
RN 7440-09-7 HCAPLUS
CN Potassium (8CI, 9CI) (CA INDEX NAME)

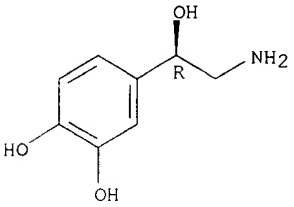
K

IT **50-67-9**, biological studies **51-41-2 51-61-6**, biological studies
RL: BIOL (Biological study)
(release of, by brain cortex, carbachol and amino acids effect on)
RN 50-67-9 HCAPLUS
CN 1H-Indol-5-ol, 3-(2-aminoethyl)- (9CI) (CA INDEX NAME)

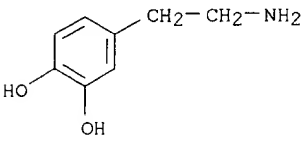


RN 51-41-2 HCAPLUS
CN 1,2-Benzenediol, 4-[(1R)-2-amino-1-hydroxyethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 51-61-6 HCAPLUS
CN 1,2-Benzenediol, 4-(2-aminoethyl)- (9CI) (CA INDEX NAME)

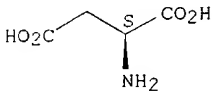


IT **56-12-2**, biological studies **56-84-8**, biological studies **56-86-0**, biological studies
RL: BIOL (Biological study)
(release of, by brain cortex, carbachol and monoamines effect on)
RN 56-12-2 HCAPLUS
CN Butanoic acid, 4-amino- (9CI) (CA INDEX NAME)

$H_2N-(CH_2)_3-CO_2H$

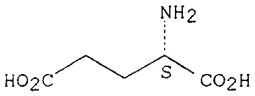
RN 56-84-8 HCAPLUS
CN L-Aspartic acid (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 56-86-0 HCAPLUS
CN L-Glutamic acid (9CI) (CA INDEX NAME)

Absolute stereochemistry.

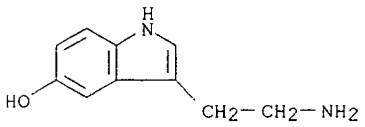


=> d bib abs hitstr l30 8

L30 ANSWER 8 OF 10 HCAPLUS COPYRIGHT 2000 ACS
AN 1985:500188 HCAPLUS
DN 103:100188
TI Effects of 250 mg% ethanol on monoamine and amino acid release from rat striatal slices
AU **Murphy, J. M.**; Cunningham, S. D.; McBride, W. J.
CS Sch. Med., Indiana Univ., Indianapolis, IN, 46223, USA
SO Brain Res. Bull. (1985), 14(5), 439-42
CODEN: BRBUDU; ISSN: 0361-9230
DT Journal
LA English
AB A single i.p. injection of 2.5 g EtOH [**64-17-5**]/kg into the rat increased the striatal levels of DOPAC [**102-32-9**] and homovanillic acid (HVA) [**306-08-1**] 1 h later to 133 and 141% of control values, resp. Blood alc. concns. at this time were approx. 250 mg%. The increased striatal tissue levels of DOPAC and HVA found after i.p. administration did not appear to be due to a direct effect of EtOH on the efflux of these 2 metabolites or on the release of dopamine (DA) [**51-61-6**] since in vitro studies with striatal slices demonstrated that 250 mg% EtOH had no effect on the endogenous release of DOPAC, HVA, or DA. However, EtOH did enhance the K+-stimulated, Ca2+-dependent release of glutamate [**56-86-0**] and aspartate [**56-84-8**] from striatal slices to 168 and 214% of control values, resp. The release of glutamate and aspartate from slices of midbrain (minus colliculi) was also increased by 250 mg% EtOH. On the other hand, the release of **GABA** [**56-12-2**], norepinephrine [**51-41-2**], and 5-HT [**50-67-9**] did not appear to be significantly altered by 250 mg% EtOH. The in vitro findings have led to the hypothesis that the elevated DOPAC and HVA levels obsd. in the striatum following an acute i.p. injection of 2.5 g/kg of EtOH are due to increased release of DA produced by the excitatory actions of glutamate (and(or) aspartate) on dopaminergic neurons.
IT **64-17-5**, biological studies
RL: BIOL (Biological study)
(amino acids and monoamines release by striatum response to)
RN 64-17-5 HCAPLUS
CN Ethanol (9CI) (CA INDEX NAME)

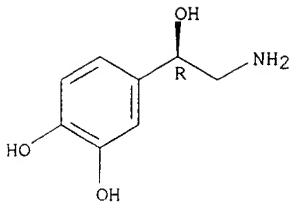
H_3C-CH_2-OH

IT **50-67-9**, biological studies **51-41-2 51-61-6**, biological studies **56-12-2**, biological studies **56-84-8**, biological studies **56-86-0**, biological studies **102-32-9 306-08-1**
RL: BIOL (Biological study)
(release of, by striatum, ethanol effect on)
RN 50-67-9 HCAPLUS
CN 1H-Indol-5-ol, 3-(2-aminoethyl)- (9CI) (CA INDEX NAME)

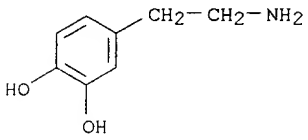


RN 51-41-2 HCAPLUS
CN 1,2-Benzenediol, 4-[(1R)-2-amino-1-hydroxyethyl]- (9CI) (CA INDEX NAME)

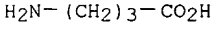
Absolute stereochemistry.



RN 51-61-6 HCAPLUS
CN 1,2-Benzenediol, 4-(2-aminoethyl)- (9CI) (CA INDEX NAME)

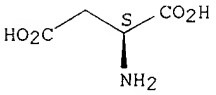


RN 56-12-2 HCAPLUS
CN Butanoic acid, 4-amino- (9CI) (CA INDEX NAME)



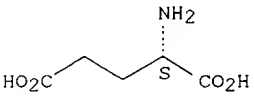
RN 56-84-8 HCAPLUS
CN L-Aspartic acid (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

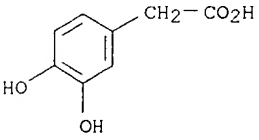


RN 56-86-0 HCAPLUS
CN L-Glutamic acid (9CI) (CA INDEX NAME)

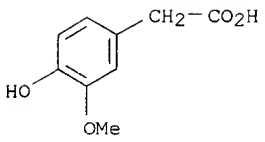
Absolute stereochemistry.



RN 102-32-9 HCAPLUS
CN Benzeneacetic acid, 3,4-dihydroxy- (9CI) (CA INDEX NAME)

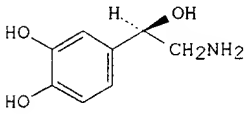


RN 306-08-1 HCAPLUS
CN Benzeneacetic acid, 4-hydroxy-3-methoxy- (9CI) (CA INDEX NAME)


CH2— CO2H
HO
OMe

=> d bib abs hitstr l30 9

L30 ANSWER 9 OF 10 HCAPLUS COPYRIGHT 2000 ACS
AN 1983:210479 HCAPLUS
DN 98:210479
TI In vitro release of endogenous monoamines and amino acids from several CNS regions of the rat
AU McBride, W. J.; Flint, R. S.; Ciancone, M. T.; **Murphy, J. M.**
CS Sch. Med., Indiana Univ., Indianapolis, IN, 46223, USA
SO Neurochem. Res. (1983), 8(2), 245-57
CODEN: NEREDZ; ISSN: 0364-3190
DT Journal
LA English
GI



I

AB The in vitro release of endogenous norepinephrine (I) [**51-41-2**] dopamine (DA) [**51-61-6**], 5-HT [**50-67-9**], **GABA** [**56-12-2**], glutamate (GLU) [**56-86-0**], aspartate (ASP) [**56-84-8**], glycine (GLY) [**56-40-6**], taurine (TAU) [**107-35-7**], and alanine (ALA) [**56-41-7**] from superfused slices of cerebral cortex (CTX), striatum (STR), hippocampus (HIP), hypothalamus (HYPO), midbrain (MB), thalamus (THAL), nucleus accumbens (ACC), pons-medulla (PM), and spinal cord (SC) was studied. Under resting conditions or with 60 nM K+ in the absence of Ca2+, there was little or no release of I, DA, 5-HT, **GABA**, GLU, or ASP from any region. In most regions, there was a measurable resting release of ALA, GLY, and TAU; of these 3 amino acids, only GLY in the PM and SC showed an increased release in the 60 mM K+ plus 2.5 mM Ca2+ medium. In 8 of the regions studied, the release of both **GABA** and GLU was stimulated by 60 mM K+ in the presence of 2.5 mM Ca2+. For the amino acids, no reliable data were obtained for release from the ACC because of its small size. The highest amt. of K+-stimulated, Ca2+-dependent release of **GABA** was found with slices from the HYPO, THAL, and MB, whereas the highest amt. of GLU was released from slices of STR, HIP, and CTX. In those regions where reliable levels of K+-stimulated, Ca2+-dependent release of ASP were obsd. (STR, CTX, and THAL), the amt. of ASP was 5-fold lower than the value for GLU. A K+-stimulated, Ca2+-dependent release of I, DA, and 5-HT was obsd. for all 9 central nervous system (CNS) regions studied. The highest release of DA occurred from slices of CTX, STR, and ACC; that of I was found in the HYPO and ACC; and that of 5-HT occurred in the HYPO. The data (1) do not support a transmitter role for ALA and TAU in the CNS, (2) support a major transmitter function for GLY only in the PM and SC, and (3) support a transmitter role for **GABA**, GLU, I, DA, and 5-HT in the CNS regions examd. (with the exception of **GABA** and GLU in the ACC where no data were obtained).

IT **7440-70-2**, biological studies
RL: BIOL (Biological study)
(amino acid and monoamine release by brain and spinal cord in response to)
RN 7440-70-2 HCAPLUS
CN Calcium (8CI, 9CI) (CA INDEX NAME)

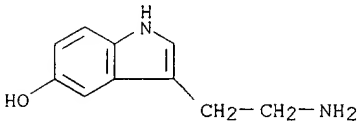
Ca

IT **7440-09-7**, biological studies
RL: BIOL (Biological study)

(amino acid and monoamine release by brain and spinal cord induction by)
RN 7440-09-7 HCAPLUS
CN Potassium (8CI, 9CI) (CA INDEX NAME)

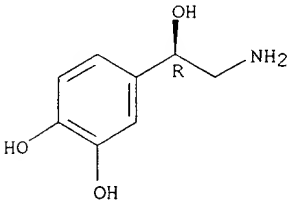
K

IT **50-67-9**, biological studies **51-41-2 51-61-6**, biological studies **56-12-2**, biological studies **56-40-6**, biological studies **56-41-7**, biological studies **56-84-8**, biological studies **56-86-0**, biological studies **107-35-7**
RL: BIOL (Biological study)
(release of, by brain and spinal cord)
RN 50-67-9 HCAPLUS
CN 1H-Indol-5-ol, 3-(2-aminoethyl)- (9CI) (CA INDEX NAME)

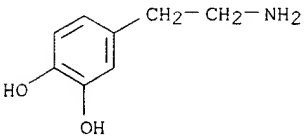


RN 51-41-2 HCAPLUS
CN 1,2-Benzenediol, 4-[(1R)-2-amino-1-hydroxyethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



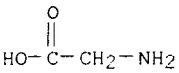
RN 51-61-6 HCAPLUS
CN 1,2-Benzenediol, 4-(2-aminoethyl)- (9CI) (CA INDEX NAME)



RN 56-12-2 HCAPLUS
CN Butanoic acid, 4-amino- (9CI) (CA INDEX NAME)

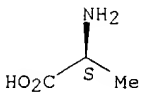
$H_2N-(CH_2)_3-CO_2H$

RN 56-40-6 HCAPLUS
CN Glycine (8CI, 9CI) (CA INDEX NAME)



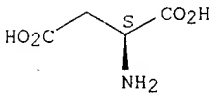
RN 56-41-7 HCAPLUS
CN L-Alanine (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



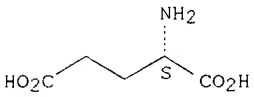
RN 56-84-8 HCAPLUS
CN L-Aspartic acid (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

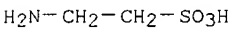


RN 56-86-0 HCAPLUS
CN L-Glutamic acid (9CI) (CA INDEX NAME)

Absolute stereochemistry.



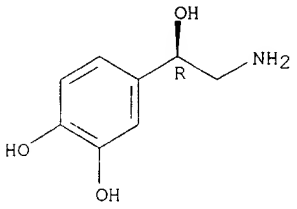
RN 107-35-7 HCAPLUS
CN Ethanesulfonic acid, 2-amino- (9CI) (CA INDEX NAME)



=> d bib abs hitstr l30 10

L30 ANSWER 10 OF 10 HCAPLUS COPYRIGHT 2000 ACS
AN 1979:538073 HCAPLUS
DN 91:138073
TI **GABA**-mediated behavioral inhibition during ontogeny in the mouse
AU **Murphy, James M.**; Meeker, Rick B.; Porada, Kenneth J.; Nagy, Z. Michael
CS Dep. Psychol., Bowling Green State Univ., Bowling Green, OH, 43403, USA
SO Psychopharmacology (Berlin) (1979), 64(2), 237-42
CODEN: PSCHDL; ISSN: 0033-3158
DT Journal
LA English
AB The possibility that **GABA** systems may mediate some behavioral inhibition during early development was investigated. Mice 9-100 days old were injected with the **GABA**-elevating agent aminooxyacetic acid (AOAA) and tested for behavioral activity. High levels of locomotor activity characteristic of immature control mice were attenuated following AOAA injection, whereas AOAA had little effect on the activity of adult mice. Moreover, AOAA produced a period of rebound hyperactivity for young but not for adult mice. Although **GABA** systems may mediate early behavioral inhibition, coordination between excitatory and inhibitory capacities apparently matures slowly. In a 2nd expt. a dopamine .beta.-hydroxylase inhibitor prevented rebound hyperactivity in young mice pretreated with AOAA, suggesting that the excitatory component may be mediated by noradrenergic systems.
IT **51-41-2 56-12-2**, biological studies
RL: BIOL (Biological study)
(locomotor behavior in development in relation to)
RN 51-41-2 HCAPLUS
CN 1,2-Benzenediol, 4-[(1R)-2-amino-1-hydroxyethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 56-12-2 HCAPLUS
CN Butanoic acid, 4-amino- (9CI) (CA INDEX NAME)

$H_2N-(CH_2)_3-CO_2H$